Record of Telephone Conversation, October 13, 2011 PM - MenHibrix

Submission Type: BLA Submission ID: 125363/0 Office: OVRR Product:
Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine
Applicant:
GlaxoSmithKline Biologicals
Telecon Date/Time: 13-Oct-2011 03:23 PM Initiated by FDA? No
Telephone Number: jody.a.gould@gsk.com
Communication Categorie(s):
1. Information Request
Author: KIRK PRUTZMAN
Telecon Summary:
By Kirk Prutzman at 10:55 am, Oct 14, 2011

GSK discussion points and questions to CR Items 4, 8, 10, 15, 19, and 21.
FDA Participants: KIRK PRUTZMAN, JOSEPH TEMENAK, DAVID STATEN,
ELIZABETH SUTKOWSKI
Non-FDA Participants: JODY GOULD Trans-BLA Group: No
Related STNs: None Related PMCs: None Telecon Body:
GSK sent the following preliminary responses and questions to CR Letter Items 4, 8, 10, 15, 19, and 21.

Item 4:
The Comparability Protocols (CPs) provided in response to Item 82 for changes in reference standards are inadequate for the purposes of reporting such changes in your Annual Report. Please address the following deficiencies in the CPs:
  a. **Most of the CPs have acceptance criteria of less than 10% differences in results generated with new and old reference standards. However, the CPS for the Free TT Content and Identity**
     assays contain qualification criteria stating that comparability between the old and new
     standard is demonstrated if the results are -(b)(4)-. Such a large variability in the calibration of new standards is not acceptable. Please revise the criteria for calibrating new standards for the Free TT Content and Identity assays.
  b. **Even 10% differences between new and old reference standards can cause problems, particularly when qualifying a new reference standard against the current standard multiple times over the life of the product. A new standard should be calibrated against the original or primary standard to avoid drift away from original value. Please develop a primary reference standard for each assay to avoid drift in calibration of reference standards over the life of the product.**
  c. **The number of qualification runs varies depending on the assay. Please run a minimum of (b)(4) qualification runs for each assay.**

d. **The number of samples run (Internal control run alone or Internal Control run with another sample) varies depending on the assay. Please run the Internal Control and (b)(4) lots of product to qualify a new lot of reference standard for each assay.**
e. **Some of the CPs contain acceptance criteria for assay validity and some do not. Please include assay acceptance/validity criteria as part of all CPs. Please verify in the qualification criteria that both the old and new standards must meet assay acceptance/validity criteria.**
f. **The CPs for Identity by (b)(4)- for Hib-TT in conjugate bulks and MenHibrix FC state that the reference is final container Hib. Please confirm that "Hib" refers to Hiberix.**

Company's approach:

The company will modify the comparability protocols provided in response to item 82 in order to address CBER's concerns mentioned in Item 4a and Item 4b. The company will propose a statistical approach that provides stringent criteria to assess the comparability between new and old references and avoid drift in calibration:

For each new reference standard, a **calibration factor** will be determined as follows:

1. The mean change (difference or ratio1) between the results generated with the new and old reference standards will be estimated based on a minimum of (b)(4) values. With such a sample size, the expected precision about the mean change will be equal to at least (b)(4) times the variability of the method. For instance, for a method variability of (b)(4), the half-width of the(b)(4) confidence interval about the mean change, which reflects the precision, will be (b)(4) maximum.

[1]A mean difference when the data follow a normal distribution, a mean ratio when the data follow a lognormal distribution

Confidential

2. A mean change will be estimated on all data obtained with the old reference: a trend analysis will be performed that covers the results obtained between T0 and the time of bridging with the new reference.

The calibration factor that will be used for the new reference will be a combination of the mean changes estimated between the old and new reference and for the old reference. In addition, the company will modify the comparability protocols to comply with requests in Q4c, d and e.

Question to CBER:

Does CBER agree that a statistical approach that avoids drift in calibration is an acceptable alternative to the use of primary references for the purpose of reporting changes in reference standards?

Item 8

Please provide data for the amounts of -----------------(b)(4)--------------------, and any other by product from the conjugation reaction for MenC-TT and MenY-TT in final product.

Company's approach:

GSK believes that the measurement of residual -(b)(4)- and by-products in final product is not relevant because:

- -(b)(4)- is converted to -(b)(4)- when --------------(b)(4)--------------- (the condition used during the conjugation reaction). In the complete response, the company will provide -(b)(4)- data in order to show that -(b)(4)- is converted into -(b)(4)- under the conjugation conditions and that other by- products are not stable or not detectable.
- The residual -(b)(4)- content has been measured in the PSY-TT and PSC-TT clinical and commercial consistency conjugate bulks by --(b)(4)--. As detailed in Modules m3.2.S.3.2 –MenC-TT and m3.2.S.3.2 –MenY-TT, the MenC-TT and MenY-TT conjugate bulks contain ----------------(b)(4)----------------- respectively, corresponding to a total -(b)(4)- content -(b)(4)- per dose for Hib-MenCY-TT 2.5/5/5 vaccine.
- The acute systemic toxicity, in vitro mutagenicity, and skin sensitisation potential of -(b)(4)- has been investigated according to relevant -(b)(4)- test guidelines, in GLP studies. Those studies were described in Module m2.6.6 and the study reports were provided in m4.2.3.7 of the BLA. These studies demonstrate that -(b)(4)- was found to be non-toxic at levels up to -(b)(4)-bodyweight given IM and up to -(b)(4)- bodyweight given orally. These non-toxic doses are high multiples of the -(b)(4)- residual dose in the Hib-MenCY-TT vaccine.

Question to CBER:
Does CBER concur with the company's position that the measurement of residual -----(b)(4)------ ----------------, and any other by product in final product is not relevant providing that (1) (b)(4) is converted in -(b)(4)- during the conjugation process and other by-products are not detected, (2) --(b)(4)-- is not stable in -(b)(4)-, (3) the residual content of (b)(4) is measured on the conjugate bulks and is well below non toxic doses evaluated in toxicity studies

Item 10d
Please modify the -(b)(4)- methods so that the -(b)(4)- data are acquired in such a way that they can be processed without baseline corrections.
Company's approach:
GSK could modify the -(b)(4)- methods so that the -(b)(4)- data are acquired without baseline corrections, however this will result in an accuracy bias of at least 118% versus an accuracy of 99-101% with a baseline correction based on current validation data. Distorted baselines are source of error in -(b)(4)- quantitative measurement. These distortions arise due to inherent properties of the -(b)(4)- technique and equipment (dead time, non linearity of the --(b)(4)-- response, -------(b)(4)--------, instrumental instabilities, etc) and not to the samples being analysed. These distortions result in inaccuracy in peak assignment and quantification. Although most of the baseline distortions can be avoided by adjusting acquisition parameters, correction of the baseline remains a common step in ------(b)(4)----- data processing Baseline distortion is exemplified in annex 1 showing spectra of a mixture of -----(b)(4)-------
1:1. In spectrum A, the baseline correction was not performed. The zero line is slightly above the
baseline of the signals and the integrals of the formate signal is equal to zero. As the formate is used as internal standard for quantification, the quantification of --------(b)(4)-------- cannot be performed. In spectrum B, the zero line is aligned to the baseline of the

signals and the formate signal is correctly integrated. The quantification of -------(b)(4)------- can be adequately performed.

The company's position is that baseline corrections of -(b)(4)- data are necessary to guarantee accurate and precise measurements of the -------------------------------(b)(4)------------------------------- content and for the identity testing. In the complete response, the company will compare data obtained with and

without baseline corrections to demonstrate the improved performance of -(b)(4)- methods when baseline corrections are applied. In addition the company will provide data demonstrating that the parameters of -(b)(4)- acquisition has been optimised to minimize baseline distortions.

Question to CBER:

Does CBER agree that providing that GSK demonstrates that the performance of the (b)(4)- measurements in terms of accuracy and precision is lower without baseline correction, the current -(b)(4)- methods

should not be modified as requested in item 10d?

Iteam 15:

We do not concur with your proposal to not add -----(b)(4)---- as a QC Release test for Final Container

MenHibrix. Please assess ------(b)(4)---- as a QC Release test.

Company's approach:

The company accepts CBER's request to assess -----(b)(4)--- via a QC Release test for the Final Container vaccine.

However, this request needs the development and full validation of a new assay, the testing of clinical and commercial lots and acceptance criteria need to be established. In the Complete Response, the company proposes to provide its development plan with detailed timing for implementation of the ------(b)(4)---- assay as a QC release test for the final container vaccine. The company proposes to submit the complete data package including validation data, results on clinical and commercial consistency lots and proposed acceptance criteria within 2 months of submitting the response to the CR Letter.

Question to CBER:

Does CBER agree that GSK can submit the development plan for the -----(b)(4)---- assay in the Complete Response and that the full data package including validation data and proposed acceptance criteria can be submitted within 2 months of the Complete Response submission without impacting the review clock?

Item 19:

We do not concur with a 36 month shelf life for MenHibrix as proposed in the BLA. Please revise the expiration date to reflect the real time stability data –b(4)--------

Company's approach:

The 36 month stability data on the commercial consistency MenHibrix final containers will be available in December 2011. In the Complete Response, the company will propose to keep a 36 month shelf-life providing that the 36 month data confirm the stability of the final product. The company proposes to submit the 36 month data within 2 months of submitting the complete response.

Question to CBER:

Does CBER agree that the 36 month stability data can be submitted within 2 months of submitting the
Complete Response without impact on the review clock?

Item 21:

We do not concur with your proposal to not place -(b)(4)- lot of polysaccharide purified bulks on stability per year. Please revise your procedures to include placing -(b)(4)- lot of polysaccharide purified bulks on stability per year.

Company's approach:

The purified PS bulks are stored in ----------------------(b)(4)------------------------ for MenY and MenC PS and their stability has been demonstrated for ----(b)(4)--- during real-time stability programs (modules m.3.2.s.2.4 related to each drug substances).

Consequently, the company considers that the stability of purified PS bulks has been fully documented. Moreover, taking into account that (b)(4) lot of Hib-TT, PSC- TT and PSY-TT commercial conjugate bulks and (b)(4) lot of commercial final container will be placed on stability per year, the company considers that the commercial stability will be adequately documented.

Question to CBER:

Does CBER agree that a commercial stability program on each drug substance and on the drug product is sufficient and that a commercial stability program on purified --------(b)(4)------- is not required?

One Page Determined Non-Releasable: (b)(4)