Request for CMC Information Email, April 25, 2014 - GARDASIL 9

RECORD OF EMAIL COMMUNICATION

Submission Type: BLA Submission ID: 125508/0 Office: OVRR

Product: Human Papillomavirus 9-valent Vaccine, Recombinant
Applicant: Merck Sharp & Dohme Corp.

Telecon Date/Time: 25-Apr-2014 03:02 PM
Initiated by FDA? Yes
Telephone Number: N/A (email)
Communication Category: Information Request

Author: Laura Montague
Telecon Summary: Request for CMC information - ----------(b)(4)----------, cLIA, and (b)(4) assay information

FDA Participants: Laura Montague
Non-FDA Participants: Alison Fisher
Trans-BLA Group: No
Related STNs: None
Related PMCs: None

Telecon Body:

From: Montague, Laura
Sent: Friday, April 25, 2014 3:02 PM
To: alison_fisher@merck.com
Cc: Khurana, Bharat
Subject: STN 125508/0; Information Request #6

Dear Alison,

We have the following requests for CMC information for BLA 125508:

1. Regarding ---------(b)(4)----------, and your response to CBER IR #1 sent on 14 Feb 2014 (response received on 20 Mar 2014):

   a. In your linearity study presented in Table Q7-6, you have presented ----------(b)(4)----------. With the information you provided, it is not

possible for us to assess if the linearity study covers the proposed range of the assay. Please provide data on the dilutions (range of concentrations) and data that were used to calculate the slope of standards and test samples corresponding to HPV types 31, 45, 52 and 58.

b. In accuracy determinations shown in Table Q7-4, ----(b)(4)---- was studied using ------(b)(4)------ corresponding to HPV types 31, 45, 52 and 58. The ----------(b)(4)---------- levels which do not cover the proposed range of the assay. Please provide data to demonstrate accuracy over the proposed range of the procedure.

2. Please provide the data demonstrating that key -----(b)(4)---- antibodies used for the ----------*(b)(4)*---- potency assay (b)(4) and the immunogenicity assay (cLIA) are "conformation- dependent and neutralizing" (for example, 3.2.S.3.1.6 p. 108 mentions ----------(b)(4)---------- assay results).

3. In 3.2.S.4.3.3 Validation of Analytical Procedures p. 30, the following statement regarding ----------(b)(4)---------- used in (b)(4) is found: ----------(b)(4)----------. Please provide details of these qualification procedures.

4. In 3.2.S.3.1.2 Elucidation of Structure and Other Characteristics (HPV Types 6/11/16/18) section 7.3, a correlation between immunogenicity and antigenicity is discussed. Are similar data available for HPV types 31/33/45/52/58? If so, please submit this information.

5. In 3.2.S.4.3.10 Validation of ---(b)(4)--- p. 11, the final assay format for the ----(b)(4)---- assay is described as ----------(b)(4)----------. Please clarify this discrepancy.

6. In the cLIA validation report (p. 15 of 125; submitted in STN125508 sequence number 0005; Question 9 Appendix 2), the following statement is found: "As part of routine testing, it is recommended that the titers from the (b)(4) control samples be trended over time." Please provide an analysis of trend over time for control samples used in the 9-valent cLIA.

7. In 3.2.S.2.5.7 Purification Process Validation (New HPV Types) p.7, the following statement is found: "Following the presentation of the process validation information, a summary of test information for lots manufactured after the process validation lots is provided to support Continued Process Verification efforts (section 13)." Is "section 13" mentioned in this document missing? Please clarify and provide missing information if available.

Please respond to this information request within two weeks. If that is not possible, please provide a timeline as to when you expect to submit the data.

Thank you,

Laura Montague
Regulatory Project Manager
FDA/CBER/OVRR
Division of Vaccines and Related Product Applications
1401 Rockville Pike Rockville, MD 20852 phone: (301)796-2640
fax: (301)827-3075, (301)827-3532