Information Request Email, February 14, 2014 - GARDASIL 9

RECORD OF TELEPHONE CONVERSATION
Submission Type: BLA Submission ID: 125508/0 Office: OVRR
Product: Human Papillomavirus 9-valent Vaccine, Recombinant
Applicant: Merck Sharp & Dohme Corp.
Telecon Date/Time: 14-Feb-2014 04:22 PM Initiated by FDA? Yes
Telephone Number: Email
Communication Categorie(s): 1. Information Request
Author: BHARAT KHURANA
Telecon Summary: Information requested by several review divisions (DVP, DBSQC, Clinical, BiMo, APLB, Labeling)
FDA Participants: Bharat Khurana
Non-FDA Participants: Alison Fisher, Merck
Trans-BLA Group: No
Related STNs: None
Related PMCs: None
Telecon Body:
The following Information Request was forwarded to the sponsor
From: Khurana, Bharat
Sent: Friday, February 14, 2014 4:22 PM
To: alison_fisher@merck.com
Cc: Montague, Laura
Subject: STN 125508/0; Information Request #1
Dear Alison,
After an initial review of your biologics license application STN 125508/0, including the amendment 125508/01, we have identified the following comments, deficiencies, and questions:

CMC

1. As discussed previously in an email on Jan 9, 2014, please submit a draft Lot Release Protocol Template by February 21, 2014.
2. For the control of GARDASIL®9, please provide the qualification report for the sterility test showing the test was qualified in accordance with ---(b)(4)--- to confirm the product matrix for the ----------(b)(4)---------- final container drug product is suitable for the intended test method. Please include the indicator microorganisms tested, their growth media and confirmation of acceptability of cfu challenge, lot numbers of conformance batches tested, and incubation conditions used in the qualification.
3. Please provide the ----------(b)(4)---------- endotoxin test qualification report demonstrating that the matrix for GARDASIL®9 ----------(b)(4)---------- final container drug product is suitable for the intended test method (in accordance with -(b)(4)-). Please include determination of maximum valid dilution, tested dilutions, positive product control percent recoveries, lot numbers, selected testing dilution and endotoxin test results in the qualification report.

4. We are in the process of setting up the (b)(4) assay in our labs. In order to calculate the (b)(4) potency of the samples, we would like to use your Excel calculation sheet for the (b)(4) assay. Please provide your current validated/verified calculation sheet used for (b)(4) calculation in support of SOP-080080159GEN.006 (---------- (b)(4)---------- 01Sep2010 as mentioned on page 28).
5. Section 3.2.R.4, ----(b)(4)------ Assay-080080159GEN.006: As per the “Note” in Section II.A.1 (pg.22), 2 and 3 (pg.23), "----------(b)(4)----------.
6. Section 3.2.R.4, ---(b)(4)--- Assay-080080159GEN.006: We notice that there is no sample criterion to ensure adequate fit of sample curves. Please consider adding a sample criterion for curve fit, or provide justification for not having this criterion.
7. Please provide the detailed data for Qualification Parameters you summarized in Table 2 of section 3.2.S.4.3.1: Validation of Analytical Procedures – ---------(b)(4)----------. Also, provide the composition of the diluent used in linearity and accuracy qualification studies you included in this table.
8. Please provide the detailed data for Qualification Parameters you summarized in Table 1 of section 3.2.P.5.3.2: Validation of Analytical Procedures – Aluminum.

CLINICAL

9. Please submit the following for the cLIA immunogenicity assay:
a. Description of the assay including overview of assay development
b. Assay validation summary
c. Assay validation report
d. Assay SOP
Some of the information above was provided in IND13447, but for the sake of completeness, it should also be included in the BLA.
10. In your immunogenicity data sets, please include a “non-parallel (NP)” flag field (Yes/No) to identify whether or not the sample exhibited non-parallelism during the 9-valent cLIA assay testing, as requested by CBER on March 01, 2012 and assured by you in response (IND13447/367, dated May 8, 2012). This information should be submitted as soon as possible.
11. Please provide line listings or tabular summaries of the cases that meet the case definition of primary efficacy endpoints. The information should include subject ID and age, study centers, vaccine administered and vaccination dates, cytology/histology findings, HPV typing results, test dates and specimens.
12. Please provide the case report forms for the cases that meet the case definition of primary efficacy endpoints.
13. In the ‘All HPV Naïve’ population, please provide a list of subjects with study pathology panel diagnosis of cervical intraepithelial neoplasia grade 2 or worse, vulvar intraepithelial neoplasia grade 2 or worse, or vaginal intraepithelial neoplasia grade 2 or worse due to any causes. For each subject, please include the subject ID, age, study center, vaccine administered and vaccination dates, and cytology and HPV results and the corresponding test dates and specimens including baseline values.

In the ‘Full Analysis’ population, please provide the same information as requested for the ‘All HPV Naïve’ population.
14. Please revise the Pediatric Plan to include a request for deferral for 16 year-old males.
15. Please provide narrative summaries of drop-outs due to adverse events or reactions for Studies V503-001, V503-005 and V503-006. If the narrative summaries were submitted in the original submission, please provide the locations for the above mentioned narrative summaries.
16. Under Module 5.2, all studies submitted to support the marketing application were listed as clinical trials not conducted under IND 13447. Actually, all studies except Study V503-009 were conducted under IND 13447. Please clarify this discrepancy.
17. For HPV persistent infection endpoints in Study V503-001, the +/-1 month visit window could allow for persistent infections of >=4 months and >=10 months to be counted as cases. Please provide the proportion of cases of persistent infection that were actually documented as >=6 months and >=12 months, respectively.
18. Please provide financial disclosure information for Study V503-009.
19. We note that five investigators reported disclosable financial interests/arrangements. We have the following requests:
a. Please provide a description of the steps taken to minimize potential bias.
b. Please provide details as to the nature of the payments to the five investigators and specify the Merck product involved for each payment.
c. Please explain why the payments to the five investigators reported by Merck via internal search are different from those reported by the investigators to Merck.
d. Please provide the number of primary efficacy cases in Study V503-001 (tabulated by HPV-4 and HPV-9 treatment arms) reported by the investigators with disclosable financial interests.
20. Please confirm if the submission contains ethnicity-, age- and gender-based subgroup analyses for primary efficacy, immunogenicity and safety endpoints for studies V503-001, V503-002, and overall. If so, please identify the locations of these analyses in the submission.
21. In each clinical study report, clinical supplies (e.g., Table 9-4 in clinical study report 001) are identified by control numbers and formulation numbers. Please provide the definition of each number type and confirm which number is lot or batch number.
22. Please provide the following information on the clinical investigators for study V503-002 sites 002-24, 002-47, and 002-49 and V503-006 site V503-006-0001:
a. Did the clinical investigator from site 002-24 conducting study V503-002 inform you of the ----------(b)(4)----------? If so, when did he inform you of the (b)(4)? Please include a timeline of your knowledge of the events related to ----(b)(4)---- and study management.
b. Was the study completed or ongoing when the ----(b)(4)---- event happened? If ongoing, were the study responsibilities transferred to another investigator? Did you collect a signed Form FDA 1572 from the new investigator? Please describe the roles of the new investigator, if applicable.
c. Did you provide a timeline to the investigator to organize the CRFs and other pertinent study data for the subjects enrolled in the V503-002 study (or each of the studies if the investigator was conducting more than one study sponsored by you) and

did the investigator send the data to you? Please describe your actions.
d. Where are the records from sites 002-24, 002-47, and 002-49 located?
e. Did you perform any additional data monitoring at V503-002 sites (002-24, 002-47, and 002-49) including applicable study drug inventories?
f. Did your study site monitoring reveal the actions taken by the investigator such as IRB notification of the events and study closure and the notification to the study enrollees about further actions such as Informed Consent revisions for follow-up?
g. Did you obtain revised Financial Disclosure certification statements from the investigator and sub-investigators when the investigator closed the study?
23. For study V503-001 and V503-002, please submit revised data tables which include columns for Site ID and the actual Subject number.

LABELING

24. The syringe and vial labels do not include a 2D bar code, but do include a designated area for the 2D bar code. Please provide the 2D barcodes as well as the GS1 (Human Readable) Information for each 2D barcode used.
25. The complete list of NDC codes for each of the labels are not listed in the "How Supplied" section and the "Packaging" sections of the SPL. Please revise your labels to include the NDCs in those sections.

ADDITIONAL

26. Do you plan to simultaneously market both Gardasil and Gardasil-9? Please briefly describe your marketing plans for both Gardasil products.

We are providing the above comments to give you preliminary notice of potential review issues. Our initial review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Please provide your responses as amendments to the BLA as soon as possible and as they become available. In your responses, please identify this information request by date and include comment numbers.

If you have any questions, please feel free to contact Ms. Laura Montague or myself at (301) 796-2640.

Thank you,
Bharat

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