Mid-Cycle Communication Telecon Summary, June 3, 2014 - GARDASIL 9

Date: June 10, 2014

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STN #: 125508/0
Application Type: BLA (Original Application)
Product Name: GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant

Subject: Summary of telecon, dated June 3, 2014, regarding Mid-Cycle Communication

Dear Dr. Fisher:

Please find attached a summary of the telecon, dated June 3, 2014, regarding Mid-Cycle Communication for STN 125508/0, for your reference. Please feel free to contact Laura Montague or myself if you have any questions.

MID-CYCLE COMMUNICATION TELECON SUMMARY

STN #: 125508/0
Application Type: BLA (Original Application)
Product Name: GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant
Proposed Indication: GARDASIL®9 is indicated in girls and women 9 through 26 years of age, and boys 9 through 15 years of age, for the prevention of specific diseases caused by the HPV types included in the vaccine
Applicant: Merck Sharp & Dohme Corp.

Meeting Date & Time: June 3, 2014, 2:30-4:00 pm
Committee Chair: Haruhiko Murata
RPMs: Bharat Khurana and Laura Montague

I. ATTENDEES

A. FDA Attendees:

Wellington Sun, DVRPA, OVRR, CBER
Tim Nelle, DVRPA, OVRR, CBER
Laura Montague, DVRPA, OVRR, CBER
Bharat Khurana, DVRPA, OVRR, CBER
Sixun Yang, DVRPA, OVRR, CBER
Nancy Miller, DVRPA, OVRR, CBER
Haruhiko Murata, DVP, OVRR, CBER
Keith Peden, DVP, OVRR, CBER
Karen Campbell, DBSQC, OCBQ, CBER
Erin Mcdowell , DIS, OCBQ, CBER
Jeremy Wally, DMPQ, OCBQ, CBER
Marion Michaelis, DMPQ, OCBQ, CBER

B. Contractor:

Christopher A. Sese, Eastern Research Group (ERG)

C. Merck Attendees:

Dicky Abraham, Director, Project Management
Paula W. Annunziato, Executive Director, Clinical Research
Ercem Atillasoy, Vice-President, Regulatory Affairs
Oliver M. Bautista, Senior Principal Scientist, Biostatistics
Ivan S.F. Chan, Executive Director, Biostatistics
Joshua Chen, Director, Biostatistics
William H. Dodge, Associate Director, Regulatory Affairs
Alison L. Fisher, Director, Regulatory Affairs
David Gutsch, Executive Director, Regulatory Affairs
Fabio Lievano, Distinguished Scientist, Drug Safety
Alain Luxembourg, Director, Clinical Research
Erin Leigh Moeller, Associate Principal Scientist, Clinical Research
Don D. Monkovic, Director, Quality
Brent Oswald, Director, Biologics & Vaccine Formula
William M. Rankin, Associate Director, Regulatory Affairs
Christine C. Roberts, Director, Clinical Research
Christine Velicer, Senior Principal Scientist, Epidemiology

II. DISCUSSION SUMMARY:

- After introducing FDA personnel attending the meeting, the member of the independent contractor team Eastern Research Group (ERG), Christopher A. Sese, was asked to introduce himself. CBER announced that ERG is tasked with assessing “the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V,” and that Christopher A. Sese will be an independent assessor and silent observer of this meeting. Thereafter, Merck was asked to introduce its attendees.

- After introductions, CBER announced that this was the Mid-Cycle Communication Telecon for Original BLA STN 125508/0, Gardasil 9. The purpose of this telecon was to provide Merck an update on the status of the review. CBER further added that we would not have an extensive discussion on any specific issues as most were not new. However, CBER would arrange a separate telecon with specific reviewers, or follow up later via email, in case Merck needed any clarifications.

- Merck requested a written summary of the review status. CBER notified Merck that a copy of the Mid-Cycle Communication Telecon Summary will be provided to them, which will include all the issues or comments that were to be discussed in this meeting.

- CBER provided the following update on the status of the review:

1. Significant issues identified by the review committee to date:

i. Validation of assays:

Validations and stability data to support the use of the diphtheria, tetanus, pertussis and meningococcal assays to assess concomitant administration of Adacel and Menactra with Gardasil 9 are not sufficient and that CBER had requested additional information under three separate requests. A response from Merck to the latest Information Request from CBER (IR #8), dated May 9, 2014, was still pending. CBER also had a t-con on May 13, 2014, to clarify our request and explain our concerns. Though the assays were reviewed previously during the approval of Gardasil, in some cases changes made to the assays since that review are not sufficiently supported, or new validation reports are not adequate to demonstrate suitable performance of the assays. The additional information that CBER had requested should be available from the

concerned laboratories as part of their routine assay monitoring and standard operating procedures.

ii. Performance Qualification of the Autoclave Sterilization of Equipment:

There is an outstanding issue regarding Performance Qualification of the autoclave sterilization of equipment used in the manufacture of the 9-valent HPV vaccine. Performance Qualification of the autoclave sterilization of equipment in --------(b)(4)-------- of Merck's -(b)(4)- Facility was previously submitted and reviewed under two CBE-30s for the quadrivalent HPV vaccine (STN 125126/2990 and STN 125126/3024). Complete response letters were issued for these CBE-30s on March 20, 2014 and the outstanding issues still need to be addressed. These issues were communicated to Merck under this BLA in the Information Request (IR #11) of May 30, 2014.

However, CBER acknowledged that Merck had proposed a pathway for resolving these issues, as discussed during a teleconference held on May 14, 2014, with DMPQ. It is also CBER's understanding that Merck intends to submit an amendment to the BLA by June 9, 2014, to include developmental data that supported use of the autoclaves in ----------(b)(4)---------- as well as protocols for completion of Performance Qualification studies. DMPQ has agreed to review and comment on the information in this amendment, and then Merck plans to complete the Performance Qualifications and submit the data from these studies by September 10, 2014.

iii. Non-Compliance with GCP at One Clinical Site:

Merck was notified that several Good Clinical Practice violations were identified at --(b)(4)(b)(6)-- clinical site (V503-001-(b)(4)(b)(6)). Although these violations were identified during the conduct of a different study, we are concerned that similar practices may have occurred during V503-001. The following information request was sent to Merck on May 20, 2014, in this regard. Merck's response to this request was pending.

a. We requested Merck to indicate whether they had conducted an internal audit of site V503-001-(b)(4)(b)(6) for protocol V503-001 or if an internal audit was planned.

b. In case an internal audit had not been conducted, Merck was requested to provide an assessment of feasibility of conducting such an audit within the time frame of the review of STN 125508.

iv. Pending Inspections of Clinical Sites and Establishment Inspection Reports:

- Inspections have been conducted at 4 clinical sites in US.

  - A three-item Form FDA 483 was issued at the clinical site in Seattle, Washington. Items listed on the 483 included incomplete informed consent/assent forms for minors enrolled in the trial, lack of verification of subject age, missing vital sign documentation for at least 10 subjects for most of the 36 study visits/subject. The Establishment Inspection Report (EIR) for this site is currently being reviewed.

- The EIR is pending receipt and review for 2 US sites.

- BiMo inspections and EIRs for the International sites in Thailand and Denmark are pending.

2. Information regarding major safety concerns:

- CBER noted increased numbers of cases of multiple sclerosis, type 1 diabetes mellitus, and Raynaud's phenomenon in the 9vHPV group as compared with the qHPV group. In the 9vHPV treatment group, there was also an increased rate of spontaneous abortions in subjects who became pregnant with an estimated date of conception (EDCn) within 30 days of any vaccination, compared with the corresponding rate in subjects who became pregnant with an EDCn not-within 30 days of any vaccination. In addition, the spontaneous abortion rate in subjects who became pregnant with an EDCn within 30 days of any vaccination was higher than the corresponding rate in qHPV treatment group. CBER expressed an interest to hear Merck's analysis of the clinical significance of these numerical imbalances. An Information request regarding these numerical imbalances will be submitted to Merck within the next few days.

3. Preliminary review committee thinking regarding risk management:

- CBER is further analyzing the safety data described above (see Item 2) to determine whether any post-marketing assessments or surveillance will be required.

4. Any information requests sent and not received:

i. Information Request #8, dated May 9, 2014, regarding validation of assays.

ii. Information Request #10, dated May 20, 2014, regarding GCP non-compliance and submission of lot release protocols for bulks of the original 4 HPV types in Gardasil, dated May 20, 2014. *(Received partial response from Merck on May 30, 2014)*

iii. Information Request #11, dated May 30, 2014, regarding facilities and equipment.

5. Any new information requests to be communicated:

- Additional information request(s) may be communicated, if needed, as the review proceeds.

6. Proposed date(s) for the Late-Cycle Meeting:

- The Late-Cycle Meeting with Merck, via a teleconference, has been scheduled for Tuesday, September 9, 2014, 1-3 PM.

- Merck was advised that they have an option of having the late cycle meeting as a face-to-face meeting and were requested to inform CBER in case they desired a face-to-face meeting.

7. Updates regarding plans for the AC meeting:

- Merck was informed that there are no plans to take this application to an advisory committee meeting at this time

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates:

- Labeling Comments to Applicant: 10-Nov-2014
- PMC/PMR Study target: 10-Nov-2014