Late-Cycle Meeting Agenda, September 8, 2014 - GARDASIL 9

125508/0: Late-Cycle Meeting Agenda

Agenda Date: September 8, 2014
Late Cycle Meeting Date: September 9, 2014
Late Cycle Meeting Time: 1:00 pm – 3:00 pm
Call-in Details: Call-in # 888-390-0683, -----(b)(4)-----
STN #: 125508/0
Submission Type: BLA (Original Application)
Product: Human Papillomavirus 9-valent Vaccine, Recombinant, GARDASIL®9
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.

I. Introduce Attendees from Merck, CBER, and ERG Contractor

II. Issues requiring resolution prior to Action Date:

A. Facility-related

i. Performance Qualification of autoclave sterilization
As stated in the Late Cycle Memo sent to Merck on August 28, 2014, CBER anticipates receiving results of the Performance Qualification in September 2014. Determination of the acceptability of the results is pending submission and review.

ii. Observation of particles in tanks used to formulate drug product
Merck and CBER participated in a telecon on September 3, 2014, to clarify several comments, including those related to the observation of particles, in CBER's information request #17, sent to Merck on August 25, 2014. CBER understands that Merck is currently preparing their full response to IR #17.

B. Sample testing and Lot Release

i. Lot Release Protocol
Merck submitted a revised LRP Template in 125508/0/32 on September 5, 2014. CBER will respond to Merck by September 19, 2014 regarding its acceptability.

ii. Samples for in-support testing
Merck will send all samples for in-support testing to CBER by September 30, 2014. Merck is asked to contact CBER prior to shipping samples.

C. Clinical

i. Possible non-compliance with GCP at clinical site in (b)(4)(b)(6)
Merck conducted an audit of (b)(4)(b)(6) clinical site in (b)(4)(b)(6) in mid-August 2014, and submitted the audit report to CBER on September 2, 2014 in 125508/0/31. CBER is preparing a follow-up information request to address questions raised by the audit report. Since receiving the report, CBER has had several meetings regarding how data from this site should be addressed in the BLA. CBER will inform Merck as early as possible regarding the resolution of this question and whether any reanalysis of data will be required of Merck.

ii. Alleged Non-compliance with GCP at clinical sites in (b)(3)(b)(4)(b)(7)
CBER sent IR #16 to Merck on July 31, 2014. Merck submitted a partial response to CBER in 125508/0/30 on August 8, 2014. CBER understands the final part of Merck's response to the IR is in route, and will be submitted to CBER very soon. Upon receipt of all information regarding the (b)(3)(b)(4)(b)(7) clinical sites, CBER will determine how data from these sites should be addressed in the BLA. CBER will inform Merck as early as possible regarding the resolution of this question and whether any reanalysis of data will be required of Merck.

D. Current Assessment of the need for risk management actions

CBER is deliberating on the most appropriate post-marketing assessment(s) to determine the significance of the observed imbalance in rates of spontaneous abortions among women who became pregnant within 30 days of vaccination with 9-valent vs. 4-valent Gardasil. Several approaches are being considered. Merck has indicated that it is planning to perform a pregnancy registry to further examine SAB in pregnant women vaccinated with 9-valent Gardasil. CBER is interested in the details of the proposed pregnancy registry design (see response to Merck agenda item IIIC below).

E. Information Requests sent with responses still pending

As of the date of this agenda, IR #17, dated August 25, 2014, is the only IR currently requiring response from Merck.

F. New Information Requests to be communicated

i. Clinical site in (b)(4)(b)(6)
CBER is preparing an Information Request to clarify items in Merck's audit report of (b)(4)(b)(6) site, which was submitted to CBER on September 2, 2014 in STN 125508/0/31. If possible, CBER will send the IR to Merck before the Late Cycle Meeting.

ii. As always, additional IRs may be forthcoming as review work continues.

G. Additional data or analyses that may be submitted

As mentioned above, CBER is concerned about clinical data at certain sites in (b)(4)(b)(6) and (b)(3)(b)(4)(b)(7). CBER may determine that it is not appropriate to use data from these sites to inform a regulatory decision. If such a determination is made, CBER will request that Merck re-analyze data and submit the reanalyses to the BLA. Depending on the scope and timing of the reanalyses, the submission could be classified as a major amendment, which would trigger an extension of the PDUFA goal date. CBER is working to achieve resolution on this issue as quickly as possible.

III. Merck Agenda Items provided September 5, 2014

A. Merck has provided our audit summary report for ----------(b)(4)(b)(6)---------- in the follow-up response to information request 10 (IR10). At the late cycle meeting, it would be very helpful to understand CBER's outstanding questions concerning the audit (if there are any) or if the information provided addresses CBER's questions with respect to --(b)(6)(b)(4)-- site to close out IR10. During the Late Cycle Meeting, discussion will return to this topic if not addressed fully during previous discussion on this topic.

B. Merck has provided a comprehensive response to IR16 (for clinical trial sites in (b)(3)(b)(4)(b)(7d)) less hard copies of informed consents, which are to be delivered to CBER by courier. At the late cycle meeting, it would be very helpful to understand CBER's outstanding questions concerning the information provided (if there are any) or if the information provided (short paper copies of ICs) closes out IR16. During the Late Cycle Meeting, discussion will return to this topic if not addressed fully during previous discussion on this topic.

C. Regarding risk management actions pertaining to spontaneous abortions (SAB) listed in CBER late cycle review memo, in the dossier and also in the response to IR13 question 1 (SAB rates in V503-001), Merck proposes a pregnancy registry to address this concern. Merck would like to understand at the late cycle review meeting if CBER concurs with this approach.

A pregnancy registry is one option under consideration in CBER's internal discussions regarding how best to address the observed spontaneous abortion imbalance. CBER's primary concern with a pregnancy registry is whether it will effectively capture pregnancies that are the subject of CBER's concern, i.e., those that begin within 30 days of vaccination with 9-valent Gardasil. CBER is interested to discuss the details of Merck's pregnancy registry design during the Late Cycle meeting and to hear Merck's perspective on how effectively the registry might answer the question of spontaneous abortion risk among women who become pregnant within 30 days of vaccination with 9-valent Gardasil.

IV. Action Items