Late-Cycle Memo, August 28, 2014 - GARDASIL 9

125508/0: Late-Cycle Memo

To: The File of STN 125508/0
Date: August 28, 2014
Re: Status of Review of 125508/0
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.

This memo was sent to Merck on August 28, 2014

1. **Current status of pending issues that will require resolution prior to Action Date:**

   A. Facility-related

   i. CBER has reviewed new developmental data and protocols for the Performance Qualification of the autoclave sterilization of equipment, and provided comments to Merck during a telecon on July 10, 2014. The results of the Performance Qualification are anticipated in September 2014, and determination of their acceptability is pending submission and review.

   ii. In their response to IR #11 submitted on June 30, 2014, Merck reported the presence of particles (residue-related and --(b)(4)--) in the tanks used to formulate the drug product. Further information on these particles was requested from Merck in an information request (IR #17), sent to Merck on August 25, 2014. A telecon to discuss the issues raised in IR #17 is planned for September 3, 2014. See also section 3C of this memo.

   B. Sample Testing and Lot Release

   Based on prior communications, CBER expects:

i. Merck will submit a revised lot release protocol template by September 5, 2014.

ii. 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 one clinical site in (b)(4)(b)(6): CBER anticipates receiving Merck's audit report on August 29. Review of that report will determine if further information or action is necessary.

ii. Alleged Non-Compliance with GCP at clinical sites in (b)(3)(b)(4)(b)(7): CBER is reviewing the information received on August 8, 2014 in amendment 30 that was sent in response to IR #16 regarding the conduct of clinical trials in (b)(3)(b)(4)(b)(7). CBER expects to receive the remainder of the response to IR #16 at Merck's earliest convenience.

2. **Current assessment of the need for risk management actions:**

   Discussions within CBER are ongoing regarding rates of spontaneous abortions in subjects who became pregnant within 30 days of vaccination with HPV vaccines. CBER will update Merck on these discussions at the late-cycle meeting on September 9, 2014.

3. **Information requests sent and not received:**

   A. IR #16, remainder of response to question 7 - Merck has responded to most of IR#16, however has not yet submitted copies of signed informed consent/assent forms.

   B. IR #10 follow-up request - In this follow-up IR sent August 20, CBER requested a report of the audit performed at ----------(b)(4)(b)(6)----------. Merck has informed CBER that the report will be submitted on August 29, 2014.

   C. IR #17 – This IR regarding facility-related issues was sent to Merck on August 25, 2014. Merck requested a follow-up telecon, which has been scheduled for September 3, 2014.

4. **New information requests to be communicated:**

   No new information requests are pending as of August 28, 2014. However, additional information requests may be forthcoming as review continues.

5. **Projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates:**

   A. Final Proprietary Name Review/Clearance: October 1, 2014

B. First Labeling Comments to Applicant: November 10, 2014

C. Identify any need for PMC/PMR (target date): November 10, 2014

6. **Status Update**

CBER presented Merck's request for a partial waiver for children from birth to less than 9 years of age to the Pediatric Review Committee (PeRC) on July 23, 2014. The PeRC agreed to waive the pediatric study requirement for ages 0 through 8 years because initiating vaccination prior to age 9 does not represent a meaningful therapeutic benefit over initiating vaccination at 9 years of age and older, and Gardasil 9 is not likely to be used in a substantial number of children in this age group. No further action related to PREA is required of Merck for this application.

7. **Merck Agenda Items**

CBER asked Merck to inform CBER by September 4, 2014 regarding items that Merck would like to include in the agenda for the Late Cycle Meeting. This will ensure that CBER has the appropriate reviewers and supervisors in attendance at the meeting. A meeting agenda will be sent to Merck on September 5, 2014. There will be an opportunity for discussion during the meeting if further topics for discussion arise.