DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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Contact:	Alison Fisher, Ph.D. Director, Worldwide Regulatory Affairs
Company Name: Address:	Merck Sharp & Dohme Corp. P.O. Box 1000, UG2D-68 North Wales, PA 19454-1009 Telephone: 267-305-6727 Fax: 267-305-6407
From:	Laura Montague Microbiologist (Regulatory) FDA/CBER/OVRR/DVRPA 10903 New Hampshire Avenue WO71, Silver Spring, MD 20993-0002 Telephone: 301-796-2640 Fax: 301-595-1244
STN #:	125508/0
Application Type:	BLA (Original Application)
Subject:	Summary of Late Cycle Meeting, held September 9, 2014

Dear Dr. Fisher:

Please find attached a summary of our Late Cycle meeting for STN 125508, held September 9, 2014. Please feel free to contact Bharat Khurana or myself if you have any questions.

LATE-CYCLE MEETING SUMMARY

STN #	125508/0
Submission Type	BLA (Original Application)
Product	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	September 9, 2014
Meeting Time	1 – 3 pm
Meeting Format	Teleconference
Committee Chair	Haruhiko Murata
RPMs	Bharat Khurana and Laura Montague

I. ATTENDEES

A. CBER

Nabil Al-Humadi, Ph.D.	OVRR/ DVRPA
Steven Anderson, Ph.D., M.P.P, Office Director	OBE
Noel Baichoo, Ph.D.	OCBQ/ DBSQC
Lokesh Bhattacharyya, Ph.D.	OCBQ/DBSQC
Karen Campbell, M.S.	OCBQ/DBSQC
Anil Choudhary, Ph.D., M.B.A.	OCBQ/DBSQC
John Eltermann, R.Ph., M.S., Division Director	OCBQ/DMPQ
Karen Farizo, M.D.	OVRR
Doran Fink, M.D., Ph.D.	OVRR/DVRPA
Marion Gruber, Ph.D., Office Director	OVRR
Patricia Holobaugh, M.S.	OCBQ/DIS
Dale Horne, Dr.P.H.	OBE/DB
Andrea Hulse, M.D.	OVRR/DVRPA
Christopher Jankosky, M.D., M.P.H., Acting Div. Deputy Director	OBE/DE
Bharat Khurana, D.V.M., Ph.D., M.B.A.	OVRR/ DVRPA
Philip Krause, M.D., Office Deputy Director	OVRR
Robin Levis, Ph.D., Division Deputy Director	OVRR/DVP
Tsai-Lien Lin, Ph.D.	OBE/DB
Dana Martin	OCBQ/DCM
Darlene Martin, M.S.	OVRR/DVRPA
LCDR Adamma Mba-Jonas, M.D., M.P.H.	OBE/DE
William McCormick, Ph.D., Division Director	OCBQ/DBSQC
Erin McDowell, B.S., B.A.	OCBQ/DIS

Loris McVittie, Ph.D., Division Deputy Director	OVRR/DVRPA
Marion Michaelis	OCBQ/DMPQ
Nancy Miller, M.D.	OVRR/DVRPA
Laura Montague, B.S.	OVRR/DVRPA
Haruhiko Murata, M.D., Ph.D.	OVRR/DVP
Timothy Nelle, Ph.D.	OVRR/DVRPA
Manette Niu, M.D., Acting Division Director	OBE/DE
Rakesh Pandey, Ph.D.	OVRR/DVRPA
Keith Peden, Ph.D.	OVRR/DVP
Mark Schwartz, J.D., Office Deputy Director	OCBQ
John Scott, Ph.D., Division Deputy Director	OBE/DB
Muhammad Shahabuddin, Ph.D.	OCBQ/DBSQC
Lisa Stockbridge, Ph.D.	OCBQ/DCM
Wellington Sun, M.D., Division Director	OVRR/DVRPA
Leslie Wagner, Ph.D.	OVRR/DBPAP
CDR Jeremy L. Wally, Ph.D.	OCBQ/DMPQ
Lihan Yan, Ph.D.	OBE/DB
Sixun Yang, M.D., Ph.D.	OVRR/DVRPA

B. Eastern Research Group (ERG)
Christopher Sese, Independent Assessor
Patrick Zhou, Independent Assessor

C. Merck
Paula Annunziato, Executive Director Clinical Research
Ercem Atillasoy, Vice President Vaccines Infectious Disease & Labeling
Ivan Chan, Executive Director Biostatistics
Josh Chen, Director Biostatistics
Alison Fisher, Director Vaccines Infectious Disease & Labeling
Dave Gutsch, Executive Director Vaccines Infectious Disease & Labeling
Robin Isaacs, Vice President Project Leadership
Fabio Lievano, Executive Director Drug Safety
Alain Luxembourg, Director Clinical Research
Erin Moeller, Associate Director Clinical Research
Bill Rankin, Associate Director CMC Regulatory
Andrew Robertson, Director Regulatory Affairs
Christine Velicer, Director Epidemiology

II. BACKGROUND

On May 19, 2014, CBER and Merck agreed to hold the late-cycle meeting for STN 125508/0 on September 9, 2014. On August 28, 2014, CBER sent the Late Cycle Memo (see Appendix A) to Merck. The memo provided an overview of significant review issues identified to date. On September 8, 2014, CBER provided a Late Cycle Meeting agenda (see Appendix B) to Merck. The agenda also included items provided by Merck on September 5, 2014.

III. DISCUSSION SUMMARY

Discussion was limited to status updates of items provided in the agenda, and to topics requiring discussion to work toward resolution.

A. Facility-related Issues

i. Performance Qualification of autoclave sterilization
CBER acknowledged receipt of the Performance Qualification results that Merck submitted in 125508/0/33 on September 8, 2014. The amendment is currently under review.

ii. Observation of particles in tanks used to formulate drug product
Merck stated that the full response to IR #17 will be submitted no later than September 30, 2014.

B. Sample testing and Lot Release
CBER reminded Merck of the importance of contacting CBER prior to shipping samples for in-support testing.

C. Clinical
A summary of the discussion concerning GCP issues at sites in (b)(3)(b)(4)(b)(6)(b)(7) is provided under item IIIG (below).

D. Current Assessment of the need for risk management actions
In regard to spontaneous abortions (SAB) associated with 9vHPV, Merck expressed confidence that a pregnancy registry is the best means of gathering more information about SAB in women who become pregnant within 30 days of vaccination with 9vHPV. Merck stated that the registry would follow the same methodology as the registry used for 4-valent Gardasil, and provided details regarding the data and information collected in that registry. CBER expressed concern that the number of women that would be included in a 9vHPV registry would be too small to be meaningful; especially for women whose pregnancies begin within 30 days of vaccination, which is the main focus of CBER's concern. CBER encouraged Merck to consider how accrual could be enhanced. CBER also asked Merck to propose targeted observational studies that could address the SAB concern. Merck reiterated that they have considered this question in the context of both Gardasil and 9vHPV over many years, and they currently have no alternate proposal. CBER expressed concern that a pregnancy registry would not include a comparator group, and Merck pointed out that the information gleaned from a 9vHPV pregnancy registry would have the added benefit of having comparator information collected in the Gardasil pregnancy registry.

This discussion ended with the agreement that Merck will provide a pregnancy registry proposal for 9vHPV that includes the following:

- the data and information about the Gardasil pregnancy registry that was conveyed to CBER during the late cycle meeting discussion
- a rationale to support Merck's assertion that a pregnancy registry is superior to other means of assessing pregnancy exposures to 9vHPV, especially exposures of pregnancies beginning within 30 days of vaccination

E. Information Requests sent with responses still pending
   i. Merck's response to IR #17 regarding the observation of particles in tanks used to formulate drug product is pending. As stated above, the submission is expected no later than September 30, 2014.
   ii. As stated above, the remaining part of Merck's response to IR #16 regarding informed consent documentation from clinical sites in (b)(3)(b)(4)(b)(7) is expected to be submitted soon.
   iii. Merck's response to CBER's follow-up to IR #10 (dated September 8, 2014) regarding GCP noncompliance issues at a site in (b)(4)(b)(6) was discussed during this meeting and is summarized under item IIIG below. Future actions to be taken by CBER and Merck in regard to this information request can be found in Section IV (Action Items).

F. New Information Requests communicated
   i. See Action Items below for new information requested at this meeting.
   ii. CBER reminded Merck that additional IRs may be forthcoming as review work continues.

G. Additional data or analyses that may be submitted
   In the Late Cycle Meeting agenda, CBER expressed concern regarding data collected at one site in (b)(4)(b)(6) and two sites in (b)(3)(b)(4)/(b)(7) due to non-compliance with good clinical practice (GCP) and informed Merck of the possibility that CBER may determine that it is not appropriate to use these data to support STN 125508/0.

   CBER and Merck began discussion of this topic with Merck addressing a follow-up information request to IR #10 sent to Merck on September 8, 2014. There were 3 items in CBER's September 8 IR to Merck.
   i. CBER requested clarification of what Merck meant by "serial order" collection of gynecological specimens. Merck explained that when gynecological specimens were collected, a swab for PCR was to be collected before cytology specimens. Merck lacks documentation that specimens were collected in that order. Merck maintained that the specimens were collected at the correct time points, and expressed that they do not have concerns about the integrity of the data collected.
   ii. CBER requested clarification regarding which elements of physical examinations were not conducted for study subjects. Merck clarified that only the general physical examinations were not conducted for a subset of subjects at the site. Gynecological examinations were conducted, and gynecological specimens were collected. Merck stated that they do not believe that study data was compromised by the lack of general physical examinations, as no data was to be captured from these exams.
   iii. CBER asked Merck to submit an overall monitoring plan for clinical sites for 9vHPV. Merck asked CBER to clarify that request. CBER and Merck discussed the type of information that CBER is looking for, and discussion of this topic ended with the agreement that CBER would provide written clarification to Merck as a follow-up to this meeting.

Merck stated that the GCP issues identified at both the (b)(3)(b)(4)(b)(6)(b)(7) sites do not affect the safety, efficacy, and immunogenicity conclusions of the 9vHPV studies.

Merck offered to submit sensitivity analyses excluding the three study sites with GCP issues. CBER accepted Merck's offer, and discussion followed to clarify the scope and details of the analyses. This discussion ended with the agreement that following the late cycle meeting, Merck will provide an outline of the data to be included in the sensitivity analyses.

H. Merck Agenda Items
Merck provided three agenda items for the late cycle meeting. All items were discussed earlier in this meeting.

IV. ACTION ITEMS

A. Merck Action Items
- The remainder of Merck's response to IR #17 will be submitted no later than September 30, 2014.
- Merck will contact CBER prior to shipping samples for lot release testing.
- Merck's response to the follow-up to IR #10 sent on September 8, 2014, will be sent to CBER as soon as possible. Merck will require CBER's written clarification of an overall monitoring plan (see CBER action items below) in order to respond fully to CBER's September 8 request.
- Merck will provide a pregnancy registry proposal as discussed in item III D.
- Merck will provide an outline of the data to be included in sensitivity analyses excluding data from the (b)(3)(b)(4)(b)(6)(b)(7) sites.

B. CBER Action Items
- CBER will send Merck written clarification to better explain CBER's request for an overall monitoring plan that was included in CBER's follow-up information request sent September 8, 2014.

V. APPENDICES

A. Late Cycle Memo, sent to Merck on August 28, 2014 (begins page 6)
B. Late Cycle Meeting Agenda, sent to Merck on September 8, 2014 (begins page 8)

Appendix A

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, passcode --(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.

Appendix B

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, passcode --(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)(6)(b)(4)
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) site in (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)(4)(b)(6) 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)(7) 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