MID-CYCLE MEETING SUMMARY

Memo Date:	May 27, 2014
To:	The File
From:	Bharat Khurana
Signature:	
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 & Time:	May 22, 2014, 2-4 pm
Chair:	Haruhiko Murata
RPMs:	Bharat Khurana and Laura Montague

CBER INVITEES/ATTENDEES

Name	**Attended**
Haruhiko Murata, DVP	Yes
Laura Montague, DVRPA	Yes
Bharat Khurana, DVRPA	Yes
Sixun Yang, DVRPA	Yes
Nancy Miller, DVRPA	Yes
Andrea Hulse, DVRPA	Yes
Jeff Roberts, DVRPA	Yes
Doran Fink, DVRPA	Yes
Nabil Al-Humadi, DVRPA	Yes
Martin (Dave) Green, DVRPA	No
Wellington Sun, DVRPA	Yes
Loris McVittie, DVRPA	Yes
Rakesh Pandey, DVRPA	Yes
Timothy Nelle, DVRPA	Yes
David Schwab, DVRPA	No
Darlene Martin, DVRPA	Yes
Robin Levis, DVP	No

Sara Gagneten, DVP	No
Keith Peden, DVP	Yes
Lokesh Bhattacharyya, DBSQC	Yes
Karen Campbell, DBSQC	Yes
James Kenney, DBSQC	Yes
Muhammad Shahabuddin, DBSQC	No
William McCormick, DBSQC	Yes
Anil Choudhary, DBSQC	Yes
Noel Baichoo, DBSQC	Yes
Mark Schwartz, OCBQ	No
Lihan Yan, DB	Yes
Amelia (Dale) Horne, DB	No
Tsai-Lien Lin, DB	Yes
Garrette Martin-Yeboah, DE	No
Lori Austin-Hansberry, DE	No
Adamma Mba-Jonas, DE	Yes
Christopher Jankosky, DE	No
Michael Nguyen, DE	Yes
Wei Hua, DE	No
Craig Zinderman, DE	Yes
Dana Martin, DCM/APLB	Yes
Lisa Stockbridge, DCM/APLB	Yes
Erin Mcdowell, DIS	Yes
Jeremy Wally, DMPQ	Yes
Laurie Norwood, DMPQ	Yes
Joseph Quander III, DMPQ	No
Cheryl Hulme, DMPQ	No
Patricia Holobaugh, DIS	No
Freyja Lynn, DBPAP	Yes
Leslie Wagner, DBPAP	Yes
Maureen Hess, OVRR	Yes
Karen Farizo, OVRR	Yes
Marion Gruber, OVRR	Yes
Anthony Lorenzo, DMPQ	Yes
Scott Norris, DBPAP	No
Douglas Pratt, DVRPA	No
Christopher Joneckis, CBER ADRM	Yes

I. AGENDA

The purpose of this meeting was to discuss:

i. discuss the progress of the review,
ii. identify and present substantive issues, and plans to address substantive issues,
iii. plan the remainder of the review including dates for further deliverables and interactions,

iv. obtain supervisory feedback, and,
v. agree upon the material to be communicated in the Mid-Cycle Communication.

II. BACKGROUND

BLA STN #125508/0] (DATS #574313)] was submitted by Merck Sharp & Dohme Corp. on December 10, 2013 and received by CBER on December 10, 2013. The BLA is intended to support the following indications:

GARDASIL® 9 is indicated **in girls and women 9 through 26 years of age** for the prevention of the following diseases caused by the HPV types included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
    - Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS).
    - Cervical intraepithelial neoplasia (CIN) grade 1.
    - Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
    - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.
    - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

GARDASIL®9 is indicated **in boys 9 through 15 years of age** for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
    - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

III. REVIEW COMMITTEE

The review committee members are as follows:

Name	Division	Role
Haruhiko Murata	DVP	CMC Reviewer and Chair
Laura Montague	DVRPA	RPM
Bharat Khurana	DVRPA	RPM
Sixun Yang	DVRPA	Clinical reviewer
Nancy Miller	DVRPA	Clinical reviewer
Nabil Al-humadi	DVRPA	Tox reviewer
Lokesh Bhattacharyya	DBSQC	QC Reviewer
Karen Campbell	DBSQC	QC Reviewer
James Kenney	DBSQC	QC Reviewer
Muhammad Shahabuddin	DBSQC	QC Reviewer

Lihan Yan	DB	Biostats Reviewer
Adamma Mba-jonas	DE	Epidemiology Reviewer
Dana Martin	DCM/APLB	Labeling reviewer
Erin Mcdowell	DIS	BIMO
Jeremy Wally	DMPQ	Product Quality and Facility Reviewer
Cheryl Hume	DMPQ	Development of protocol template
Leslie Wagner	DBPAP	D&T Assay Reviewer
Freyja Lynn	DBPAP	Pertussis and Meningococcal Assay Reviewer

IV. REVIEW TIMETABLE

Review Milestone	Target Due Date	Completion Date
Received:	10-Dec-2013	
Committee Assignment:	24-Dec-2013	
First Committee Meeting:	31-Dec-2013	
Filing Meeting:	24-Jan-2014	
Filing Action:	07-Feb-2014	07-Feb-2014
Deficiencies Identified:	22-Feb-2014	
VRBPAC Determination:	24-Feb-2014	
PeRC Scheduling:	25-Apr-2014	
Mid-Cycle Reviewer Report Due*:	22-May-2014	16-May-2014
Mid-Cycle Meeting:	26-May-2014	22-May-2014
Mid-Cycle Communication:	11-Jun-2014	03-June-2014
Primary Final Reviews Due*:	2-Aug-2014	
Internal late-Cycle Meeting:	22-Aug-2014	
Late-Cycle Meeting:	10-Sep-2014	
Complete Inspections:	2-Oct-2014	
PMC/PMR/SWG Determination:	7-Oct-2014	
Labeling Meetings begin (internal):	9-Oct-2014	
Final Review Addendum Due*:	10-Nov-2014	
Labeling Comments to Applicant:	10-Nov-2014	
Finalize Lot Release Protocol:	6-Nov-2014	
Initiate Compliance Check:	10-Nov-2014	
PMC Study target	10-Nov-2014	
Finalize Approval Package:	18-Nov-2014	
Action Due Date (ADD):	10-Dec-2014	
After Action Meeting:	Jan-24-2015	

*These milestone dates are for review memos with supervisory concurrence.

V. REPORT AND DISCUSS

1. Reviewer Reports.

- Reviewer Reports were collected, compiled and forwarded to the Mid-Cycle Meeting attendees on May 20, 2014.
- Each Reviewer presented his/her report to the review committee and management.
- The increased rates of multiple sclerosis (MS), type 1 diabetes mellitus (DM1), Raynaud's phenomenon, and spontaneous abortions (SABs) observed in the 9vHPV as compared to the qHPV group was discussed at length. Clinical, Pharmacovigilance and Biostatistical reviewers presented their preliminary assessments and plans regarding higher rates of these adverse events among recipients of 9vHPV including:
    - A presentation of the rates of these AEs observed in historical placebo controls in the [quadrivalent] Gardasil program and the general population; rates were similar to those observed in the 9vHPV group.
    - A discussion of using mini Sentinel post-marketing to evaluate MS, DM1, Raynaud's phenomenon and other neuroinflammatory diseases of interest.
    - A discussion of possibly needing a post marketing requirement (PMR) study to evaluate the higher rate of spontaneous abortions.
    - Management noted that numerical imbalance does not necessarily connote a safety signal, the data should be further evaluated before a conclusion is made that the observations represent a safety signal that would require a PMR. The reviewers were asked to further analyze the data to determine if the observed imbalances are true imbalances, if these are chance events, or if any bias or confounding is involved. The reviewers will analyze the cases to compare temporal relation, background rates, etc.
    - Additional information may be requested from the applicant, if needed, regarding the observed imbalance. The applicant will be asked to interpret these findings.
    - Pharmacovigilance Reviewers explained that general safety surveillance for HPV9 could be conducted in FDA's Sentinel Program for a set of pre-specified health outcomes of interest. However, this study would be designed for monitoring and would not necessarily provide definitive results (e.g., attributable risk) for any single outcome. MS in particular, with insidious and often unclear onset, may be difficult to study in Sentinel. Sentinel is not able to study spontaneous abortions at this time.

2. ***Will Discipline Review Letters be issued (for PDUFA V Program submissions)? [Individual Reviewers, Chair]***

   - Discipline Review Letter will not be issued by any of the reviewers.
   - Chris Joneckis (CBER ADRM) confirmed that we are not required to issue a Discipline Review Letter.

3. ***If the application will be discussed at an Advisory Committee, potential issues for presentation.***

   - Not Applicable. The application will not be discussed at VRBPAC.

4. ***Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) are needed. [Clinical Reviewer, Chair]***
   Will there be a Title IX PMR requiring SWG review?

   Title IX PMRs may be needed for evaluation of spontaneous abortions. Clinical, Biostatistical and Pharmacovigilance Reviewers' assessments are preliminary and ongoing. Further information gathering and review is necessary to evaluate if SA numerical imbalance constitutes a signal.
   - The reviewers were reminded that if a PMC, PMR or REMS is needed, the approval letter will need to be drafted in a timely manner (by November 1, 2014) because it has to undergo review by several committees.
   - The OVRR Safety Working Group Representative should be notified of any potential PMR/PMC or REMS as soon as they are identified.

5. ***National Drug Code (NDC) assignments to product/packaging.***

   - CBER SPL was contacted on May 23, 2014 to obtain NDC assignments to product/packaging.

6. ***Proper naming convention.***

   - Applicant's proposed name doesn't follow the convention as established by Cervarix and Gardasil.

     - **Gardasil 9**:
       Human Papillomavirus 9-valent Vaccine, Recombinant
     - **Gardasil:**
       Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant
     - **Cervarix:**
       Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant.

- We will ask the Applicant to list the HPV Types included in the vaccine in their proposed proper name during labeling negotiation.

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. [Facility Reviewer, Product Reviewer, BiMo Reviewer]

- **Facility Inspection:** No facility inspections are planned. However, there are outstanding issues regarding validations of autoclave sterilization that would likely need to be addressed for approval of this BLA. Performance Qualification of the autoclave sterilization of equipment used in the manufacture of the 9-valent HPV vaccine 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 have not been addressed to date. These issues were communicated to Merck under this BLA in the Information Request (IR #11) of May 30, 2014.

  A telecon with Merck to discuss their strategy for addressing the issues for these autoclave sterilization validations, as described in Merck's email of May 9, 2014, was held on May 14, 2014. Merck plans to submit an amendment to the BLA by June 9, 2014, to include developmental data to support use of the autoclaves in ----------(b)(4)---------- as well as protocols for completion of Performance Qualification studies. DMPQ agreed to review and comment on the information in this amendment, and then Merck intends to complete the Performance Qualifications and submit the data from these studies by September 10, 2014.

- **BIMO Inspections:** Four national sites (Georgia, Florida, Washington & Pennsylvania) and 2 international sites (Thailand & Denmark) were selected. Inspection has already been conducted at the four national sites; however, inspection is pending at the international sites (planned for late May and June).

  No Form FDA 483s were issued to the sites in Augusta, Georgia and Tampa, Florida. The final inspection classification for the clinic site in Tampa, Florida is NAI (No Action Indicated). The investigation of Tampa Florida site revealed that the CI was on the applicant's advisory board and helped develop many of the protocol requirements for the studies.

  The BIMO inspection at Site in Seattle, Washington, has been completed. A three-item Form FDA 483 was issued. Items listed on the 483 included incomplete informed consent forms for minors enrolled in the trial, lack of verification of subject age, missing vital sign documentation for over 10 subjects for 1-3 study visits.

  The EIRs are pending receipt from the inspection at the sites in Augusta, Georgia, Seattle, Washington, and Carnegie, Pennsylvania.

VI. CONFIRM

8. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) if discrepancies were found per SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements. If not complete, indicate date it will be completed.

- Haru Murata is currently working on obtaining the Components Information Table at this time.
- At the end of the meeting, Chris Joneckis explained the purpose of the Components Information Table, and provided advice for obtaining the table.

9. New facility information is included in the application, requiring implementation of regulatory job aid JA 910.01: Facility Data Entry. If not complete, indicate date it will be completed.

- No new facilities are included in this application.

10. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

- The review of the lot release protocol will be completed by September 19, 2014.
- Preliminary IV (b)(4) testing with samples (expired with recent test results) sent in January is going well and is almost complete.
- The applicant plans to submit the in-date samples for in-support testing in the 3rd quarter (July-Sep, 2014).
- DBSQC announced that their offices and labs are scheduled to move to White Oak in August. This move schedule is not anticipated to impact DBSQC's testing of samples.
- The testing plan will be completed by October 10, 2014, provided there is no outstanding labeling or testing issue that prevents its approval.

11. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid JA 900.01: Unique Ingredient Identifier (UNII) Code for additional information.

- Request for UNII codes was initiated on April 23, 2014.

12. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision. Remind the review committee that PeRC forms have to be submitted two weeks in advance of scheduled PeRC meeting.

- Waiver request for boys and girls less than 9 years of age.
- PeRC is scheduled for July 23, 2014

- Additional timelines in preparation for PeRC:
  - Completed forms to CRB BC and DD (Andrea and Wellington) – June 25
  - Completed (and reviewed by CRB BC and DD) forms to OVRR Rep – July 2
  - Please note that PeRC forms have to be submitted two weeks in advance of scheduled PeRC meeting, i.e., by July 9, 2014.
  - **Presentation is scheduled for July 23, 2014.**

13. Reach agreement on information to be included in the Mid-cycle communication with the applicant

- A draft template of what we are planning to discuss in the Mid-cycle communication with Merck was presented to the attendees.
- Reviewers will edit the comments to be included in the Mid-Cycle Communication
- Supervisory concurrence on the Mid-cycle communication content will occur by review of the Mid-cycle meeting summary (the Mid-cycle communication summary is included as part of the Mid-cycle meeting summary).

VII. REVIEW:

14. Major target and milestone dates from RMS/BLA.

- Discussed in Section IV. REVIEW TIMETABLE

15. Discuss pending dates of targets and milestones (e.g. late-cycle meeting, Advisory Committee, labeling discussion).

- Internal Late-Cycle Meeting: August 22, 2014
- Late-cycle meeting: September 9, 2014 (scheduled)
- No VRBPAC
- Labeling Meetings (internal) begin: 9-Oct-2014

16. The status of the review for each discipline, inspection, EIR. If any primary reviews have not met the target date, provide the date the review will be completed. Include any consult disciplines.

Review discipline	Reviewer (Division)	Target Review Completion Date/Status
CMC	Haru Murata (DVP)	Mid-July, 2014
Clinical	Sixun Yang (DVRPA)	July 2, 2014 *(1 outstanding IR, dated May 20, 2014)*
Non-clinical	Nabil Al-Humadi (DVRPA)	Completed *(pending Supervisor's concurrence)*

QC (test methods)	Lokesh Bhattacharya (DBSQC)	June 3, 2014
QC (lot release)	Karen Campbell (DBSQC)	Oct. 10, 2014 (applicant to forward the in-date samples by 3rd quarter, and 1 outstanding IR, dated May 20, 2014)
QC (sterility & endotoxin)	James L. Kenney (DBSQC)	Completed (memo uploaded on April 23, 2014)
QC (test methods)	M. Shahabuddin (DBSQC)	Aug. 15, 2014
Biostatistics	Lihan Yan (DB)	July 21, 2014
Pharmacovigilance	Adamma Mba-Jonas (DE)	June 1, 2014
Labeling	Dana Martin (APLB)	PNR-acceptable
BIMO inspections	Erin McDowell (DIS, BIMO)	Pending Inspections & EIRs
Facilities & Equipment	Jeremy Wally (DMPQ)	Pending response to IR, dated May 30, 2014)
Bioassay (pertussis & meningococcal)	Freyja Lynn (DBPAP)	Pending response to IR, dated May 9, 2014)
Bioassay (diphtheria & tetanus)	Leslie Wagner (DBPAP)	Pending response to IR, dated May 9, 2014)

17. ***Establish a labeling review plan and agree on future labeling meeting activities.***

    - First Internal labeling Meeting: Oct. 9, 2014

VIII. ADDITIONAL DISCUSSION ITEMS

- **<u>Clinical site closure:</u>**
  In a separate file, FDA became aware that GSK is closing the site of ----------(b)(4)(b)(6)-- for multiple violations including:
  1) Violations of GCP with regard to obtaining informed consent
  2) Backdating, copy and pasting clinical assessments/visit notes, medical charts completed days after subject visits
  3) Lack of evidence that PI was providing adequate oversight or was even directly involved in the conduct of the study

----(b)(4)(b)(6)---- is also involved in V503-001 at site (b)(4)(b)(6) for 9vHPV vaccine BLA (Gardasil 9)

- It appears that 247 subjects received 9vHPV vaccine and 248 received 4vHPV vaccine at this site in study V503-001.
- In V503-001, at site (b)(4)(b)(6), two subjects contributed to the cases in the primary analysis: 1 in the HPV9 group (AN 18149) and 1 in the HPV4 group (AN 69498).
- In the All HPV-naïve population, at site (b)(4)(b)(6), there were 0 cases in the HPV9 group and 3 cases in the HPV4 group (68110, 20740, and 69498 – the last also in the primary analysis).

The following information request was sent to Merck (May 20, 2014):

1. It has come to CBER's attention that issues were identified regarding non-compliance with Good Clinical Practice for an investigational product (not 9vHPV) being studied at the clinical site of -----(b)(4)(b)(6)----- (V503-001-(b)(4)(b)(6)). In review of study V503-001, we note that 495 subjects/14215 subjects in V503-001 were vaccinated with the mid-dose 9vHPV vaccine or qHPV at this site (3.48% of subjects).
    a. Please indicate whether Merck has conducted an internal audit of site V503-001-(b)(4)(b)(6) for protocol V503-001 or whether an internal audit is planned.
    b. If an internal audit has not been conducted, please provide an assessment of feasibility of conducting such an audit within the time frame of the review of STN 125508.

IX. ACTION ITEMS

- Reviewers will edit the comments to be included in the Mid-Cycle Communication and forward to RPMS and Chair by Thursday, May 29, 2014.
- Supervisory concurrence on the Mid-cycle communication content will occur by June 2, 2014, by review of the Mid-cycle meeting summary (the Mid-cycle communication template is included as part of the Mid-cycle meeting summary)
- The reviewers were asked to further analyze the data to determine if the observed imbalances are true imbalances, if these are chance events, or if any bias is involved. The reviewers will analyze the cases to compare temporal relation, background rates, etc.
- Additional information may be requested from the applicant, if needed, regarding the observed imbalance and applicant will be asked for their interpretation of the data.
- The applicant will be asked to list the HPV Types included in the vaccine in their proposed proper name during labeling negotiation.
- The Primary final reviews (reviewed by supervisor but not necessarily with signed concurrence) are due to RPMs on Aug. 2, 2014. This review may or may not be uploaded on the EDR at this time. If any IR is pending response or review, the reviewers may either modify their primary reviews before finally uploading on the EDR (by Nov.

10, 2014) or they may attach an addendum to their primary final reviews before uploading on the EDR.

- RPMs will convey to Merck that they may have a face-to-face late-cycle meeting, if they so desire.

X. Mid-cycle Communication:

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 we have requested additional information under three separate requests. Your response to the latest Information Request (IR #8), dated May 9, 2014, is still pending CBER receipt. We 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 we have requested should be available from the 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)---------- 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 have not been addressed to date. These issues were communicated to Merck under this BLA in the Information Request (IR #11) of May 30, 2014.

However, we acknowledge that you proposed a pathway for resolving these issues, as discussed on a teleconference held on May 14, 2014, with DMPQ. We also understand that it is your intention to submit an amendment to the BLA by June 9, 2014, to include developmental data that supports 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:

It has come to our attention 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 is pending CBER receipt.

a. Please indicate whether Merck has conducted an internal audit of site V503-001-(b)(4)(b)(6) for protocol V503-001 or whether an internal audit is planned.

b. If an internal audit has not been conducted, please 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. <u>Information regarding major safety concerns</u>:

- We have noted increased numbers of cases of multiple sclerosis, type 1 diabetes mellitus, and Raynaud's phenomenon in the 9vHPV group as compared to 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 to 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. We will be interested to hear your 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. <u>Preliminary review committee thinking regarding risk management</u>:

- We are 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.
- Please note that you have an option of having this late cycle meeting as a face-to-face meeting. If you desire a face-to-face meeting, please let us know.

7. Updates regarding plans for the AC meeting:

- 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

Attachments:

1) Information Request #8, dated May 9, 2014, regarding validation of assays

(Pending response from Merck)

From: Montague, Laura
Sent: Friday, May 09, 2014 10:37 AM
To: alison_fisher@merck.com
Cc: Khurana, Bharat
Subject: STN 125508/0; Information Request #8 (related to IRs 4 and 7)

Dear Alison,

We have reviewed the validations and stability data submitted for the assays to assess immune responses to Adacel and Menactra, including the amendment received 8 May 2014. We find these data to be insufficient to demonstrate the performance of the assays to support concomitant administration in study Protocol 005. We acknowledge that the assays were reviewed during the approval of Gardasil, however in some cases changes made to the assays since that review are not sufficiently supported, or new validation reports not adequate to demonstrate suitable performance of the assays. In order to verify that the assays performed adequately during the testing of samples for Protocol 005, we are requesting additional information. The information to respond to comments 1 and 2 should be available from the laboratories as part of their routine assay monitoring and standard operating procedures. Comments 1 and 2 supersede CBER comment 1 in Information Request #7.

1. Please provide the algorithm for batching samples for analysis to prevent bias. Please also describe the means by which assay operators are blinded as to the subject, study group and time point for each sample.

2. Please provide the following information to demonstrate that the assays were adequately controlled during sample testing for Protocol 005.
    a. A description of the system suitability criteria used to accept or reject assay runs including the limits for each criterion and the basis for each criterion.
    b. The trending or tracking data for control samples run in each assay as part of the system suitability. Please include all data, including those from assays that were rejected.

3. Please provide the reverse cumulative distribution curves for pre and post immunization for both groups for the diphtheria, tetanus, pertussis and meningococcal antigens. Please plot all curves for a given antigen on the same figure for ease of comparison between pre and post and between study groups.

4. If you intend to use these assays to assess responses to diphtheria, tetanus, pertussis and meningococcal antigens in future Phase 3 studies, we recommend you address the gaps in the validations. Our detailed review of the validations submitted to the BLA will be provided to you in response to your submission of Protocol 005 in your IND 13447. Please acknowledge.

Thank you,

Laura Montague
Regulatory Project Manager
FDA/CBER/OVRR
Division of Vaccines and Related Product Applications
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phone: (301)796-2640
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2) Merck's email on Performance Qualification of Autoclaves (dated May 19, 2014)

From: Fisher, Alison L [mailto:alison_fisher@merck.com]
Sent: Monday, May 19, 2014 11:18 AM
To: Montague, Laura; Khurana, Bharat
Cc: Hoath, Cathy; Rankin, _William M. (RAS-B)
Subject: Autoclave Update: V503

Hi Laura and Bharat,

In March, Merck received two Complete Response Letters following review of two CBE-30's to support use of autoclaves in ----------(b)(4)---------- facility. Data in those supplements was also included in the V503 BLA. Two weeks ago, a strategy for generating new data to address the concerns was proposed. Attached below is a summary sent to Marion Michaelis, Ellen Huang and Jennifer Schmidt in FDA DMPQ summarizing the current state and a strategy for resolution.

The strategy was discussed in detail on Thursday, May 1st and a final agreement on the path forward was reached with Marion ~ May 14. On or before June 9th, Merck plans to submit an amendment to the V503 BLA to contain developmental data to support use of the autoclaves in ----------(b)(4)---------- as well as protocols for completion of Performance Qualification studies. The information in the amendment will be reviewed within a week, to determine whether the testing planned for Performance Qualification is sufficient to meet current expectations. It is Merck's intent to submit a second amendment containing the data from Performance Qualification, on or before September 10th.

I am communicating this to you prior to CBER's mid cycle review for your awareness. Cathy is the subject matter expert and lead at Merck on this. You may reach out to Cathy and Bill directly as needed with any questions you have and please cc me to keep me in the loop.

Regards

Alison

3) 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
(Pending response from Merck)

From: Montague, Laura
Sent: Tuesday, May 20, 2014 5:54 PM
To: alison_fisher@merck.com
Cc: Khurana, Bharat
Subject: STN 125508/0; Information Request #10

Dear Alison,
We have the following information requests regarding your supplement 125508.

1. It has come to CBER's attention that issues were identified regarding non-compliance with Good Clinical Practice for an investigational product (not 9vHPV) being studied at the clinical site of ----(b)(4)(b)(6)---- (V503-001-(b)(4)(b)(6)). In review of study V503-001, we note that 495 subjects/14215 subjects in V503-001 were vaccinated with the mid-dose 9vHPV vaccine or qHPV at this site (3.48% of subjects).
   (a) Please indicate whether Merck has conducted an internal audit of site V503-001-(b)(4)(b)(6) for protocol V503-001 or whether an internal audit is planned.
   (b) If an internal audit has not been conducted, please provide an assessment of feasibility of conducting such an audit within the time frame of the review of STN 125508.
2. Please clarify how you intend to submit the lot release protocols for bulks of the original 4 HPV types in Gardasil. Will you be submitting to 125126 or 122508, or both?

Thank you,
Laura Montague
Regulatory Project Manager
FDA/CBER/OVRR
Division of Vaccines and Related Product Applications
phone: (301)796-2640
fax: (301)595-1244
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4) Information Request #11, dated May 30, 2014, regarding facilities and equipment
(Pending response from Merck)

From: Khurana, Bharat [mailto:Bharat.Khurana@fda.hhs.gov]
Sent: Friday, May 30, 2014 12:20 PM
To: Fisher, Alison L
Subject: STN: 125508/0: Information Request #11

Dear Alison,

We have the following information requests regarding your supplement 125508:

1. Please provide a list of all new pieces of equipment that are used for the manufacture of the 9-valent HPV vaccine, including a brief description of each item, the building and room number where the each items is located, and the manufacturing step(s) that each item is used.

2. Regarding the syringe used to supply the 9-valent HPV vaccine:

    a. Please confirm that the syringe (barrel, stopper and rod) is the same as the syringe used for the licensed quadrivalent HPV vaccine.

    b. Please provide a summary of the syringe performance and functionality testing that has been completed.

3. We reference your email of May 9, 2014, containing a plan to address the performance qualifications for autoclave sterilization of equipment used during manufacturing of the 9-valent HPV vaccine in ----------(b)(4)----------, and our acceptance of this plan during the telecon of May 14, 2014. In your planned submissions to address our concerns, please be sure to address the following items:

    a. Regarding the performance qualification for sterilization of equipment used during manufacturing of the 9-valent HPV vaccine in autoclaves ----------(b)(4)---------- in ---(b)(4)--- using load patterns ----------(b)(4)----------:

        i. Please provide the results of preliminary performance qualification studies (i.e., studies that you have designated as developmental) that are scientifically sound and valid to support the identification of worse case equipment challenge items for further performance qualification studies. The protocols for these studies should include:

            1. Run validity criteria consistent with the further performance qualification studies. (i.e., the number of allowed failed thermocouple probes).

            2. Defined evaluation criteria for critical assessments. For example, if you choose to use "mock" biological indicators to evaluate potential interferences of ----------(b)(4)----------, you must have defined evaluation criteria and provide data supporting the acceptability of their use. Alternatively, actual biological indicators with a defined acceptance criterion of no growth can be used.

            3. Consistent load configurations requirements. For example, if maximum load configurations are specified, then all runs (except for the evaluation of the minimum load) should be performed under the same conditions.

        ii. Please provide the results of further performance qualification studies that support microbial lethality and reproducibility of your production load configurations. The following concerns should be addressed:

            1. If the results of the preliminary performance qualification studies, conducted as described above, change the challenge items in the

maximum and minimum loads as well as the identity of the worst case load selected in the performance qualification studies, then these studies should be repeated using the new challenge items and worst case loads.

2. Your protocol should have an evaluation criterion to verify that the chosen worst case load configuration for reproducibility studies was worst case as compared to the other load configuration types chosen for one run confirmatory studies.

3. Since you intend to use a production autoclave cycle with ----------(b)(4)----------, the following additional information should be provided:

   a. ----------(b)(4)----------.

   b. ----------(b)(4)----------.

iii. Please provide a production SOP which includes the following information:

1. Instructions for preparation of your final validated production load configurations.

2. ----------(b)(4)----------

iv. Please provide the portion of the batch record for the most recently manufactured batch of the 9-valent HPV vaccine that describes the sterilization of equipment in autoclaves ----------(b)(4)---------- in -(b)(4)- using load

patterns ----------(b)(4)----------, and includes the actual loads used, the actual cycle parameters used, and copies of the full cycle hardcopy autoclave run printouts, as well as a description of any differences between the load pattern/cycle used for this batch and the load pattern/cycle used for the performance qualification.

b. Regarding the performance qualification for sterilization of equipment used during manufacturing of the 9-valent HPV vaccine in autoclaves ----------(b)(4)---------- in ---(b)(4)--- using load patterns ----------(b)(4)----------:

   i. Please provide the results of preliminary performance qualification studies (i.e., studies that you have designated as developmental) that are scientifically sound and valid to support the identification of worse case equipment challenge items for further performance qualification studies. The protocols for these studies should include:

      1. Run validity criteria consistent with the further performance qualification studies. (i.e., the number of allowed failed thermocouple probes).

      2. Defined evaluation criteria for critical assessments. For example, if you choose to use "mock" biological indicators to evaluate potential interferences of ----------(b)(4)----------, you must have defined evaluation criteria and provide data supporting the acceptability of their use. Alternatively, actual biological indicators with a defined acceptance criterion of no growth can be used.

      3. Consistent load configurations requirements. For example, if maximum load configurations are specified, then all runs (except for the evaluation of the minimum load) should be performed under the same conditions.

   ii. Please provide the results of further performance qualification studies that support microbial lethality and reproducibility of your production load configurations should be provided. The following concerns should be addressed:

      1. If the results of the preliminary performance qualification studies, conducted as described above, change the challenge items in the maximum and minimum loads as well as the identity of the worst case load selected in the performance qualification studies, then these studies should be repeated using the new challenge items and worst case loads.

      2. Your protocol should have an evaluation criterion to verify that the chosen worst case load configuration for reproducibility studies was worst case as compared to the other load configuration types chosen for one run confirmatory studies.

3. Since you intend to use a production autoclave cycle with ----------(b)(4)----------, the following additional information should be provided:

    a. ----------(b)(4)----------.

    a. ----------(b)(4)----------.

iii. Please provide a production SOP which includes the following information:

    1. Instructions for preparation of your final validated production load configurations.

    2. ----------(b)(4)----------

iv. Please provide the portion of the batch record for the most recently manufactured batch of the 9-valent HPV vaccine that describes the sterilization of equipment in autoclaves ----------(b)(4)---------- in ----(b)(4)---- using load ----------(b)(4)----------, and includes the actual loads used, the actual cycle parameters used, and copies of the full cycle hardcopy autoclave run printouts, as well as a description of any differences between the load pattern/cycle used for this batch and the load pattern/cycle used for the performance qualification.

4. Please provide the protocol and study report for the performance qualification of environmental monitoring in Formulation Suite (b)(4) in --(b)(4)--.

5. Regarding the validation of the cleaning of ---(b)(4)--- tanks in -------(b)(4)-------, please provide the following items:

    a. Documentation that supports that these tanks are equivalent.

    b. In follow-up to the observation of small white particles in the ----------(b)(4)----------, a copy of the Deviation Alert #135-2001-105 and Investigation #2001-135-0038.

    c. In follow-up to the observation of ----(b)(4)--- particles during studies ----------(b)(4)----------, a copy of Product Impact Assessment #57300-2001-TS-0217.

6. You indicate that ----------(b)(4)---------- located in ---------(b)(4)------ are new pieces of equipment for the 9-valent HPV vaccine. Please provide the initial sterilization validation protocol and reports for these tanks.

7. You indicate that the ----------(b)(4)---------- was re-implemented after being out-of service since its installation in (b)(4) and that modifications were made to improve the -(b)(4)-decontamination. Please clarify if the re-implementation of the ---(b)(4)--- and modifications were reviewed by CBER under a previously submitted supplement (and provide the STN), or if this is a new decontamination method being implemented for the 9-valent HPV vaccine.

8. In the report for study 8-7020-B16, describing the initial cleaning validation for HPV Type 58 in ----------(b)(4)---------- you indicate that there was a ----------(b)(4)----------, and that this study was considered invalid. Please address the following comments:

    a. Please provide a copy of the investigation report (#200171754) and a description of what actions were taken (if any) to address the apparent equipment design flaw.

    b. Since this study was considered invalid, please provide the results of a valid study that confirms your ability to clean HPV Type 58 from this equipment.

9. For the validation of ----------(b)(4)----------, you state that the validation considered a total of ----(b)(4)---- for all HPV Types. However, you state that for HPV Type 52 ----(b)(4)-- you only validated -------(b)(4)------- and that ------(b)(4)------ for HPV Types 33 and 58 were bridged to the validation for HPV Type 52. Please clarify the number of -----(b)(4)----- that is validated for HPV Type 33, 51 and 58 in ----------(b)(4)----------, and if you consider ----------(b)(4)------ validated for these HPV Types, please provide a rationale.

Please submit your response as an amendment to STN 125508/0 and as always, please feel free to contact Laura Montague or myself if you have any questions.

Thanks,
Bharat

Bharat Khurana, DVM, PhD, MBA
Microbiologist (Regulatory)

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5) Merck's email on timing of in-date final Container Samples to support Lot Release Requirements (email, dated Feb. 05, 2014).

From: Rankin, _William M. (RAS-B)
Sent: Wednesday, February 05, 2014 11:44 PM
To: Fisher, Alison L; 'Montague, Laura'
Cc: 'Khurana, Bharat'; Gutsch, David; Dodge, William H
Subject: RE: CBER Communication: V503 samples and (b)(4) Method Regional Attachment

Dear Laura,

I wanted to provide you an update regarding V503 samples that will be submitted in support of batch release requirements as described in item #2 below:

1. Merck anticipates that we will be able to submit the sample plan to support batch release requirements (-(b)(4)- final container) by the end of March 2014 or earlier.
2. Merck will supply the (b)(4) samples to support batch release requirements by the end of May 2014 or earlier.
3. Merck will provide final container samples to support batch release requirements by the end of Sept 2014.

We will update you as soon as we have definitive dates for the items above. In the meantime, please let me know if you have any questions or concerns.

Regards,
Bill

William M. Rankin • a • Associate Director, GRA Vaccines-CMC • ----------(b)(4)----------