DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Memorandum

Date: August 11, 2014

From: Leslie Wagner, Chemist, LRSP/DBPAP, Committee Member

To: STN 125508/0
GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant

Through: Mike Schmitt, Lab Chief, LRSP/ DBPAP

Subject: Complete Review Memo
Diphtheria & Tetanus Assays - Serology Review
Protocol 005, concomitant administration of Adacel® and Menactra®

Sponsor: Merck, Sharp & Dohme Corp.

Product and Indication: GARDASIL9 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.

Scope of Review: My review focused on the methodology and validation of the Diphtheria ----------(b)(4)---------- Assay and the Anti-Tetanus IgG ELISA to quantitate the amount of Diphtheria Toxin neutralizing antibodies and anti-Tetanus antibodies in human serum. This memo will provide documentation of both my initial review of the original submission and my final review and assessment based on additional information received in response to Information Requests (IR) on April 21 (Amend. 9), April 24 (Amend. 10), May 8 (Amend 12), May 22 (Amend 15), and June 6, 2014 (Amend 17).

Review of the data and assay information for responses to pertussis components of Adacel was conducted by another reviewer.

OVERALL CONCLUSION:
The immunoassays used to measure the antibody response to the diphtheria and tetanus components of Adacel are adequate for the purposes for which they were used in this application. Demonstration of acceptable performance of the assays is essential in order to include concomitant administration to the label because immunogenicity data provided the primary evidence supporting concomitant administration of the first dose of 9-valent HPV vaccine with Menactra and Adacel.

On December 12, 2013 Merck submitted an Application for approval of a new Biologics License Application (BLA) for GARDASIL9 (Human Papillomavirus 9-valent Vaccine, Recombinant). I have reviewed all documents relating to immunoassay performance of the diphtheria and tetanus assays for Merck's BLA STN 125508/0; the clinical data, assay validation reports and data supporting assay performance for the time period in which samples from P005 were tested indicate the assays were performing as expected.

Serologic data in support of the study appear to have been generated in assays adequate for that use. I recommend approval of the application.

SUMMARY:
Merck submitted a BLA for licensure of GARDASIL9 (Human Papillomavirus 9-valent Vaccine, Recombinant). As part of the labeling, Merck would like to state that GARDASIL 9 may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]. In order to support labeling for concomitant administration with meningococcal and TdaP vaccines, Merck submitted data from a study comparing separate versus concomitant administration of Menactra and Adacel with Gardasil9.

The Diphtheria ----------(b)(4)---------- Assay was used to quantitate the amount of Diphtheria Toxin neutralizing antibodies and the Tetanus IgG ELISA was used to quantitate the amount of anti-Tetanus antibodies in human serum. These assays were performed by ----------(b)(4)----------.

This study (Protocol V503-005) was an open-label, randomized, multicenter, comparative study to evaluate the tolerability and immunogenicity of the concomitant administration of the first dose of 9vHPV vaccine with Menactra and Adacel versus the administration of 9-valent HPV vaccine non concomitantly with Menactra and Adacel. The study was designed to enroll 1240 healthy, preadolescent and adolescent boys and girls, 11 to 15 years of age. The subjects were stratified by gender (1:1 ratio) and randomly assigned to 1 of 2 vaccination groups in a 1:1 ratio. Subjects in Group 1 received the 9vHPV vaccine and Menactra and Adacel administered concomitantly on Day 1. Subjects in Vaccination Group 2 received the 9vHPV vaccine on Day 1 and Menactra and Adacel at Month 1. Subjects in both vaccination groups received the second dose of the 9vHPV vaccine at Month 2 and the third dose at Month 6. Serum samples were obtained from subjects in Group 1 immediately prior to vaccination at Day 1, Month 1, and Month 7. Serum samples were obtained from subjects in Group 2 immediately prior to vaccination on Day 1, and at Month 1, Month 2, and Month 7. Sera were analyzed to determine the antibody levels to the vaccine components.

Primary Immunogenicity Objectives regarding Menactra and Adacel:
• To demonstrate that Menactra administered concomitantly with Adacel and a first dose of the 9-valent HPV vaccine induces noninferior immune responses with respect to seroconversion percentages to Neisseria meningitidis serogroups A, C, Y, and W-135 compared with the administration of Menactra concomitantly with Adacel
• To demonstrate that Adacel administered concomitantly with Menactra and a first dose of the 9-valent HPV vaccine induces noninferior immune responses to diphtheria, tetanus, and pertussis compared with the administration of Menactra concomitantly with Adacel.

Primary Immunogenicity Hypotheses regarding responses to diphtheria or tetanus antigens:
The percentages of subjects who achieve the World Health Organization (WHO)-defined protective anti-diphtheria and anti-tetanus titer of ≥0.1 IU/mL one month post vaccination in subjects receiving Adacel concomitantly with Menactra and a first dose of

the 9-valent HPV L1 VLP vaccine will be non inferior to the percentages in subjects receiving Adacel concomitantly with Menactra . (Each vaccine component will be analyzed separately. The statistical criterion for non inferiority requires that the lower bound of the two-sided 97.5% confidence interval for the difference [Concomitant Group minus Non-concomitant Group] in percentages be greater than -10 percentage points for the diphtheria and tetanus component, i.e. excluding a 10 percentage points decrease.)

Results:
Responses to tetanus and diphtheria antigens

Table 11-3 presents the proportion of subjects in the PP population with diphtheria and tetanus titers ≥0.1 IU/mL at 4 weeks post vaccination of Menactra and Adacel with associated 97.5% CIs by vaccination group. Nearly 100% of subjects in both the Concomitant Group and the Non-concomitant Group achieved a diphtheria titer and tetanus titer ≥0.1 IU/mL at 4 weeks following vaccination with Menactra and Adacel. The table shows that non inferiority of diphtheria and tetanus titer responses in the Concomitant Group, relative to the Non-concomitant Group was established at 4 weeks post vaccination with Menactra and Adacel.

The reverse cumulative distribution curves are discussed below regarding Merck's responses to IR 8 May 2013 (#8) but indicate no substantive difference between the curves between Groups A and B. No unusual or aberrant data were noted in the line listings.

REVIEW:
For each item below, I summarize issues identified during my initial review and those from the pertussis and meningococcal assay reviewer that were common to all assays; provide the wording for questions that were proposed for inclusion in an Information Request to the sponsor and comment on the additional information provided in response to the Information Request.

REVIEWER COMMENTS TO ORIGINAL SUBMISSION:
The sponsor submitted summaries of all the serologic assays that were used for this study; detailed information regarding the procedures, performance characteristics, validation reports, and continued performance over time was not included.

QUESTIONS FOR INFORMATION REQUEST#4 (7 April 2014):

1. Please provide the complete validation reports for the assays to quantitate antibody to the diphtheria, tetanus, pertussis and meningococcal antigens.

2. Please provide data that support the continued assay performance since validation and through the testing of the samples from Protocol 005.

REVIEWER COMMENTS ON THE RESPONSE TO IR#4, QUESTION'S 1 & 2:
The following documents were received in response to the IR in amendment 0.9:

- Validation Report ---(b)(4)--- Assay of Diphtheria Toxin in Sera, for SOP PDL-9486, Ed. 10 (Doc. No.: REP-8353), performed by ------(b)(4)------; Effective Date Report: November 9, 2009.
- Trend report of the diphtheria antibody assay stability for the antitoxin control --(b)(4)--; Covering the time period samples for V503-005 were tested (February – June 2011); generated by ------(b)(4)-------.
- Trend report of the tetanus antibody assay stability for the low and high controls [lot number unspecified]; Covering the time period samples for V503-005 were tested (January – May 2011); generated by ------(b)(4)-------.

The validation report and other supporting documents for tetanus were received in amendment 0.10:

- Validation Report for Human Tetanus antitoxin by (b)(4), SOP #QA8510; performed by -----(b)(4)-----; Edition 6 Effective Date 03/04.
- Standardization report for tetanus standard (b)(4), REP-8558; Effective date Feb 19, 2010.
- Standardization report of low control (b)(4) & high control -(b)(4)-, REP-8658; Effective date march 22, 2010.
- PQ Report for the use of --------(b)(4)-------- in the Human Tetanus Antitoxin by (b)(4) Assay, REP-8419; Effective date December 9, 2009.

These documents were reviewed in the context of supporting study endpoints for this application in Study P005.

<u>Assay to quantitate diphtheria antitoxin</u>:
Diphtheria antitoxin is measured in a ----------

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

---.

The most important issue identified in the validation for the anti-diphtheria assay was the limited data to support the accuracy and precision of the assay at the lower limit of quantitation (LLOQ). Other issues include incorrect analysis of precision and accuracy and insufficient detail in the report. However, assuming the assay was run under controlled conditions, the provided data do not indicate any substantive issues

with the quality of the data generated using the assays. ----------
---

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

----------.

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

The stability data found in “Trend report of the diphtheria antibody assay stability for the antitoxin control --(b)(4)--; Covering the time period samples for V503-005 were tested (February – June 2011)” consisted of charts generated from monthly analysis of the assays. The data showed numerous excursions outside control limits and all were biased low. Because of these findings, these data were insufficient to demonstrate the stability of the assay during the period samples from study P005 were tested.

Conclusion: The response for the anti-diphtheria assay is inadequate to demonstrate assay stability. Additional information will be required. See the requests for additional information under the listing of the Information Request #8 below.

Assay to quantitate tetanus antitoxin:
This assay is an ----------

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

----------.

The information submitted in support of the Tetanus assay validation contained some inconsistencies between the method used during validation and the method used to test samples for protocol 005. Supporting documents for the study, such as calculation

method and reference standard calibration, are substantially different than the version indicated in the validation report. Additional details about the assay will be needed in order to conclude that the assay is suitable for use to test samples for Protocol 005.

The stability data found in "Standardization report of low control ---(b)(4)--- & high control ---(b)(4)---, REP-8658; Effective date march 22, 2010", consisted of charts generated from monthly analysis of the assays. The data showed no aberrant data with any points exceeding control limits. The assay appears to be stable for the period when samples for P005 were tested.

Conclusion: The response is inadequate because of the uncertainty of the validation status of the procedure used to test samples. Significant changes to the test method appear to have occurred since the original validation and data have not been provided to ensure the original validation attributes have been maintained following the introduction of new procedures. Additional information will be required. See the requests for additional information under the listing of the Information Requests below.

Based on the gaps in the validation data and assay stability identified, the following IR was sent to the sponsor.

QUESTIONS FOR INFORMATION REQUEST#7 (25 April 2014):
We acknowledge the receipt of your responses to our Information Request #4, dated April 7, 2014, regarding validation of assays to quantitate antibody to the diphtheria, tetanus, pertussis and meningococcal antigens, which you had submitted via gateway as amendments #09 and #10, dated April 21, 2014 and April 24, 2014, respectively. As we review these amendments, we have the following requests for information:

1. In order to sufficiently support the use of the diphtheria, tetanus, pertussis, and meningococcal assays for their intended purposes we are requesting you provide additional information for the IgG ELISAs for tetanus toxin, pertussis toxin, filamentous haemagglutinin, pertactin and fimbriae, toxin -----(b)(4)---- assay for diphtheria toxin, and for the serum bactericidal assays for the meningococcal groups A, C, W-135 and Y. Please provide for each assay in a readable file format a listing of the assays performed to generate the data for samples from Protocol 005. Please include assay dates, operators and run numbers. For each assay please provide the values for all parameters used to assess system suitability (assay acceptance) including quality control samples, reference curve parameters, bacterial cell counts and any other measure used to assess assay performance. Please include the assays that were rejected due to quality control issues.
2. For the tetanus assay: Please provide the dates that samples for protocol 005 were tested and the version(s) of the SOP that were used during validation and during testing of samples for P005. If updates to the SOPs have occurred since validation, please summarize differences that have occurred with each version. This should include the procedure(s) for the calculation of results that were in use during these times. Please specifically address the following inconsistencies that

were identified in your response to IR#4 (Amendment 10) with respect to the assay protocol that was used during validation as well as the calculation method used to generate reportable values.

a. The report for standardization of Human Tetanus Standard -(b)(4)- (Doc No REP-8558) states that the reference was tested using SOP PDL-9539; this is different than the SOP that was used during validation (QA8510).
b. The calculation method described in the validation report (Test No. QA8510), based on a ----------(b)(4)----------, differs from the method described in supporting document REP- 8419 (PQ report for the use of -----(b)(4)------- in the Human Tetanus Antitoxin By (b)(4) Assay), which uses a ------(b)(4)------ model. REP-8419 also mentions that the plate layout, sample dilution, and number of calibrator points used in the current version of the test method differ substantially from the previous version SOP.

REVIEWER COMMENTS ON THE RESPONSE TO IR#7, QUESTIONs 1&2
The following responses and documents were received in response to the IR in amendment 12 (8 May 2014):

Documents received:

- SOP 8510, edition 7.0, Human Tetanus Antitoxin by (b)(4) authored by -------(b)(4)--; effective 25-Jul-2007
- SOP PDL-9539, edition 8.0, Human Tetanus Antitoxin by (b)(4); effective from 09-Feb-2010 through 19-Jul-2012

Question 1 - Merck indicated by email that they were unlikely to be able to provide the information requested in IR #7 in short timeframe due to the nature of record keeping at the contract laboratory sites, especially for the pertussis assays.

Conclusion: Recognizing the limitations of the availability of the data, the request was simplified and refocused. Critical quality control data were again requested. Analyses of the clinical data in the form of reverse cumulative distribution curves were requested, so that any anomalies in the data might be identified in the absence of specific assay information. See IR #8 below.

Question 2 – Merck confirmed that the validated version of anti-tetanus SOP is different than the one used to test samples for study P005. Revalidation of the procedure with these changes was not performed, instead ----------(b)(4)----------", using the new procedure (SOP PDL-9539, ed 8.0) and compared the results to those generated by the originally validated procedure (SOP QA8510, ed 7.0). Review of the two versions of the SOP revealed several significant changes to the test method that have occurred since validation. Most importantly the algorithm used to calculate results has changed from a ----------(b)(4)----------, potentially affecting assay attributes determined during the original validation. As part of the review of the potential impact of the change in calculation

method, several issues with the existing validation report was identified. Upon discussion with the review committee, the specific gaps and issues will be included in a letter to the sponsor in the context of the IND in which the relevant study (Protocol 005) was reviewed. The letter will also recommend that all the gaps be addressed before the assays are used for future Phase 3 studies generating data that will be used in the label or to base regulatory action.

It should be noted that during the change in methodology from edition 7.0 to 8.0, the SOP nomenclature changed from QA8510 to PDL-9539.

Conclusion: Despite the lack of data to support revalidation of the updated version SOP (ed 8.0), the anti-tetanus assay is suitable for the intended purpose of this study demonstrating non-inferiority of concomitantly administered Menactra and Adacel with the first dose of 9vHPV vaccine. This is based on the fact that all samples for study P005 were tested using the same version of the SOP and the robust anti-tetanus responses from both groups A and B that were at least > 20 times the assay LLOQ at four weeks post-vaccination. Thus even if moderate differences exist between versions of the test method will not affect interpretation of study outcomes for tetanus response.

QUESTIONS FOR INFORMATION REQUEST#8 (9 May 2014):
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.

Merck responded to IR #8 in amendments 0.15, 0.17 and 0.27.

REVIEWER COMMENTS ON THE RESPONSE TO IR#8, QUESTIONS 2 & 3
In response to CBER comment 2.a (Amendment 0.15):
Merck verified that for all the assays the SOPs provided in response to IR #4 are the appropriate SOPs in place during sample analysis.

In response to CBER comment 2.b (Amendment 0.15):
Tetanus and diphtheria assays: Merck indicated that records have been requested from (b)(4) and would be submitted on a rolling basis as they are available.

In response to CBER comment 2.b (Amendment 0.17):
Tetanus and diphtheria assays: Merck provided the control performance data of the tetanus assay for the time period samples for study P005 were run, including invalid results. Data indicate the assay was in a state of control during the testing of study samples. The sponsor indicated that the diphtheria trending previously submitted to CBER (IR4 Question 2, Attachment #2) was confirmed by (b)(4) to have the invalid runs included. According to the SOP an assay is invalid if the control is outside of reference limits; as noted above in response to IR#4, the data indicate a bias because all the excursions outside of control limits were below the lower limit. A stable assay would have controls that fall randomly about the mean and we would expect excursions outside control limits in both directions, especially since this controls concentration level is well above the LLOQ. Several possible explanations for these responses include assay drift or incorrect assignment of limits. It should not have an impact on the interpretation of results of this study because the results are biased low and therefore would underestimate response rates. This would not affect study outcomes because the anti-tetanus response at 4 weeks post-vaccination for groups A and B were > 10 times the clinically relevant cut-off level ---(b)(4)---. However this bias will be included in the follow up as part of the re-validation effort under the sponsor's IND for this study.

In response to CBER comment 3 (Amendment 0.15):
Merck provided the reverse cumulative distribution curves as requested. The curves indicate that the response rates for the concomitant versus separate administration

groups are entirely overlapping with no apparent anomalous data seen. The curves support the quality of the data generated.

In response to CBER comment 4 (Amendment 0.15):
Merck will either address the issues raised in CBER's review or find alternate validated assays for any future concomitant use Phase 3 studies.

Conclusion: The responses to comments 1-4 are adequate.

Recommendation

While gaps in the validation reports for the assays to assess responses to Adacel were identified, the additional data submitted, including the control data, indicate that the assays were performing appropriately during analysis of the samples from Protocol 005. Specifically the assays are considered acceptable for the following reasons: 1) the lack of any data that would indicate that the assays were not performing adequately, 2) the absence of any indication that the assays are unstable, 3) the absence of any data in the study that are unusual or anomalous, 4) the internally controlled design of the study and 5) the use of the assays to determine changes in immunogenicity rather than primary efficacy. I recommend that the labeling for concomitant administration of Gardasil9 with Menactra and Adacel be approved.