MEMORANDUM

Date August 6, 2014

RE: Administrative File for STN: 125508/0

From Anil Choudhary, Ph. D., DBSQC, HFM- 680
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Through William M. McCormick, Ph.D., Director, DBSQC, HFM-680

Cc Haruhiko Murata, Chair, DVP
Laura Montague, DVRPA

Subject: Review of Analytical Methods (1.----------(b)(4)---------- and (2) ----------(b)(4)- for Biologics Licensure Application (BLA) for Gardasil® Nanovalent: Human Papillomavirus Nonavalent (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; *S. cerevisiae*) L1 Capsid Virus Like Particle Vaccine with Alum Adjuvant (V503).

Recommendation: Approval

Summary of review:

This BLA was submitted by Merck on December 10, 2013 (STN# 125508) for approval of Gardasil® Nanovalent: Human Papillomavirus (HPV) Nonavalent (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; *S. cerevisiae*) L1 Capsid Virus Like Particle Vaccine. In this BLA, ----------(b)(4)---------- method is intended for use for the determination of ---(b)(4)--- potency, ----------(b)(4)---------- and identity (ID) of the ----------(b)(4)---------- Drug Product (DP). ---(b)(4)--- method is intended for use in the determination of the ----------(b)(4)----------. Upon review of the documents submitted in support of these methods and their validation both the methods are found to be adequately validated and suitable for use in lot release.

Submissions Reviewed

1. STN # 125508/0, dated: 12/10/13
2. STN # 125508/0.1, dated: 1/17/14
3. STN # 125508/4, dated: 3/14/14

Documents Reviewed

1. Validation Report for Human Papillomavirus Vaccine in the ----------(b)(4)---------- assay for Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 ---------(b)(4)--------, Quadrivalent, and Nonavalent Vaccine Products (31-Mar-2011).

2. Response letter from CBER (September 21, 2012) to Kimberly Duffy regarding STN 125126/2527: biologics license application (BLA) for Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant replacement (b)(4) assay.
3. Document Number: 56085-2013-TP-0003: Technical Protocol to Define Supplemental Testing for Validation of the Replacement ----------(b)(4)---------- Assay for Human Papillomavirus 9-Valent Vaccine ---(b)(4)--- Final Container Product.
4. Document Number: 56085-2013-TR-0003: Technical Report: Supplemental Testing for Validation of the Replacement ----------*(b)(4)*---------- Assay for Human Papillomavirus 9-Valent Vaccine ---(b)(4)--- Final Container Product.
5. Document Number: 56085-2013-TR-0033: Technical Report: Supplemental Evaluation of Specificity and Intermediate Precision Performance Characteristics of Method ----------(b)(4)---------- assay for HPV-like particles.
6. Validation report for HPV vaccine in the ----------(b)(4)---------- Identity Assay for HPV types 6, 11,16, 18, 31, 33, 45, 52 and 58 Vaccine Products.
7. Reference Standards or Materials – (b)(4) 3 documents.
8. Validation of Analytical Procedures(section 3.2.S.4.3.2) – ---(b)(4)---
9. Analytical Procedures (section 3.2.S.4.2.2) - ---(b)(4)---
10. Assay: Human Papillomavirus Vaccine – ----------(b)(4)----------

1. ----------*(b)(4)*---------- *Assay ---(b)(4)---*

1.1 Background :

GARDASIL®9 is a recombinant vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The L1 (major capsid) protein is expressed in recombinant systems, it self-assembles into VLPs, similar in conformation to native virions. Each 0.5-mL dose is formulated to contain 30/40/60/40/20/20/20/20/20 μg of HPV 6/11/16/18/31/33/45/52/58 L1 proteins, respectively. The final container is a sterile suspension for intramuscular injection in a single-dose vial or a prefilled syringe, to be administered as a 3-dose regimen. GARDASIL®9 targets HPV Types 6, 11, 16, and 18 also targeted by the licensed quadravalent HPV vaccine (qHPV) as well as the additional HPV Types, 31, 33, 45, 52, and 58. HPV 16 and 18 are responsible for ~70% of cases of cervical cancer. An additional ~20% of cases are due to HPV Types 31, 33, 45, 52, and 58; thus, the nine valent HPV vaccine has the potential to prevent ~90% cervical cancers. GARDASIL®9 clinical studies included in this submission were conducted in female subjects 9 to 26 years of age and male subjects 9 to 15 years of age.

1.2 Description of the ------(b)(4)------ and ID Assay:

Principle of the Procedure: ----------

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

---------- and ID assays

are modified forms of the (b)(4) assay. Because --(b)(4)--, ID, and -(b)(4)- use the same assay platform, evaluation of variation due to analyst for --(b)(4)-- also evaluates variation due to analyst for -----(b)(4)----- Identity.

Assay Method: ----------

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

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

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For Identity: The Identity assay uses the same (b)(4) assay format as a qualitative test used to confirm the presence of the appropriate HPV antigen in the sample. The same reagents and equipment as described for (b)(4) assay are used in this procedure. All steps of the Identity assay are identical to the (b)(4) assay described above, with the exception of the ----------(b)(4)----------.

1.3 Historical perspective of current submission

Prior to submission of this BLA Merck submitted a Prior Approval Supplement (PAS) on October 31, 2011, (STN 125126/2527) for replacing the currently licensed (b)(4) Assay with a new (b)(4) assay for testing potency, ID and ---(b)(4)--- of HPV for Quadrivalent (Types 6,11,16,18) Vaccine. Both new versions of (b)(4) assay ----------
----------(b)(4)----------
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This PAS has not yet been approved. CBER reviewer's concerns were communicated to the sponsor through two CR letters (March 6, 2012 and September 21, 2012). Most of the validation data from (b)(4) (Linearity and specificity studies) and ----(b)(4)---- and ID were found acceptable to DBSQC, but there were some concerns about repeatability and intermediate precision. The sponsor was requested to perform comparability study to evaluate extravariability, repeatability and intermediate precision across the range of the assay in final assay format of the method in a prospective study along with demonstration of stability of the primary standards. In response to CR#2 (September 18, 2012),

Merck submitted a Supplemental Validation Protocol (SVP) focusing on repeatability and precision. Merck has addressed most of the CR concerns in current BLA submission (STN 125508). On May 7, 2013, Merck requested a Type C meeting to discuss CMC issues to ensure CBER concurrence with Merck's plans for specification modeling, (b)(4) assay validation, and stability data rollout for the anticipated V503, Gardasil 9-valent, BLA (current submission). In this meeting, CBER agreed that SVP data for -------(b)(4)-------- method for evaluation of Quadrivalent and 9-valent DP (b)(4) would be acceptable for review. -------(b)(4)------- will be the primary method used for potency estimation of the (b)(4) DP. The sponsor agreed to not use the -----(b)(4)----- data for release and stability and that the -----(b)(4)----- data would only be used to support on-going stability studies. CBER agreed to accept data by ----(b)(4)---- method for evaluation of lot-to-lot variability for 4 HPV types (6, 11, 16 and 18) (b)(4).

1.4 Validation of Current (b)(4) Assay: For Potency, ID ----------(b)(4)----------

In this submission (STN#125508) sponsor has reported the validation data for ----------(b)(4)---------- DP of all nine HPV subtypes for the replacement (b)(4) method SOP. The validation data for the other 4 HPV subtypes (6, 11, 16, 18) is expected for replacement (b)(4) method SOP under STN#125296/2527 (pending), from SVP implementation.

Overview: ----------(b)(4)----------.

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1.4.1.2 Identity Validation

Because the (b)(4) assay is a type-specific assay, a positive response in the (b)(4) assay (one that meets the (b)(4) release specification) is considered a positive test for identity. If the (b)(4) assay is not performed, an independent identity test can be performed as described in Sec. 3.2.S.4.2.10 Analytical Procedures (b)(4)/ID/------(b)(4)------. The reagents and operating conditions are identical to those used in the (b)(4) assay. Only the ----------(b)(4)---------- differ. A summary of the parameters evaluated for the identity assay and the results is provided in Table 1.

Table 1: Summary of Parameters Evaluated During the Validation of the Identity Test

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

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1.12 Correspondence with the Sponsor

In an Email communication CBER requested Merck to provide SOP for ----(b)(4)---- assay. Merck responded on **December 11, 2013**:

"Merck would also like to discuss with CBER the commitment to provide the SOP for the ----(b)(4)---------- method description at the time of license submission. All other method descriptions have been provided as part of the license submission submitted on Dec 10, 2013 as regional attachments. This method description for the ------(b)(4)----- assay extravariability criteria is being revised as per discussion with CBER pertaining to the V501 sBLA (STN 125126/2527, date of conversation June 13, 2013). Merck will provide the version of the method description that includes the correct extravariability evaluation method by the time we submit the samples for testing. Please note that the update to the method description does not impact the text of the license sections which describe the (b)(4) assay procedure."

CBER received the --------(b)(4)------ SOP GEN080080159.006 on January 17, 2014.

On **February 14, 2014,** an IR request was sent to the sponsor with following questions:

4. We are in the process of setting up the (b)(4) assay in our labs. In order to calculate the ----------(b)(4)--- of the samples, we would like to use your Excel calculation sheet for the (b)(4) assay. Please provide your current validated/verified calculation sheet used for (b)(4) calculation in support of SOP-080080159GEN.006 (HPV ----------(b)(4)---------- Workbook v0.2 01Sep2010 as mentioned on page 28).

5. Section 3.2.R.4, --------(b)(4)-------- Assay-080080159GEN.006: As per the "Note" in Section II.A.1 (pg.22), 2 and 3 (pg.23), "----------(b)(4)----------.

6. Section 3.2.R.4, ----(b)(4)------- Assay-080080159GEN.006: We notice that there is no sample criterion to ensure adequate fit of sample curves. Please consider adding a sample criterion for curve fit, or provide justification for not having this criterion.

Merck responded on **March 14th, 2014** as follows;

Response to Question#4: Attached in Module 1.11.1 is version 1.4 of Method 080080159GEN-HPV ----------(b)(4)---------- Workbook (Q4 Appendix_1), which is now the current validated workbook used for (b)(4) calculation. Version 1.4 of the excel workbook was updated and validated for use of either benchmark 9vHPV working standard Lot ----(b)(4)---- or the 9vHPV Working Standard Lot ---(b)(4)--- provided to your laboratories on 15-Jan-2014. Per Section 3.2.S.5.4 of STN 125508/0, Working Standard Lot ---(b)(4)--- was qualified as a future working standard for ----------(b)(4)------ release and stability testing of routine manufacturing lots. Due to ongoing stability studies, laboratories within Merck and Co., Inc. have not yet transitioned from the benchmark 9vHPV Working Standard Lot ----(b)(4)---- described in Sections 3.2.S.5.2 Reference Standard or Material – (b)(4)(31/33/45/52/58) and 3.2.P.6 Reference Standards or Materials. The analytical method 080080159GEN will be updated for information specific to Lot ---(b)(4)--- prior to implementation of this Working Standard for routine release and stability testing.

Regarding your specific request for HPV ----------(b)(4)---------- Workbook v0.2 01Sep2010 as mentioned on page 28, it should be noted V0.2 of the workbook mentioned on page 28 of 080080159GEN was provided as a reference to the fixed workbook solver settings and was not intended to reflect the current version of the workbook. The current version of the workbook is 1.4 as noted above.

Response to Question#5: ----------

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

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

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Response to Question#6: Sample criterion to ensure adequate fit of sample curves is based upon ------
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----------(b)(4)----------

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Merck provided satisfactory answers to the IR and DBSQC has no further questions for the sponsor at this time.

1.13 Conclusions from Merck's Validation Reports and Response to CBER IRs for (b)(4), ID ----------**(b)(4)**----------:

The review of all of Merck's responses to CBER IRs, and Merck's submission of validation document for ---------(b)(4)-------- ID estimation assay concludes that the test method BLP 08008159GEN

procedure using ----------(b)(4)---------- has been validated satisfactorily by the sponsor for testing of ------(b)(4)------- final Gardasil nanovalent vaccine. The test method ----------(b)(4)----------. The HPV type 6, 11, 16, 18, 31, 33, 45, 52, 58 final container Drug Product and ----------(b)(4)---------- would be tested using test method BLP 08008159GEN ---(b)(4)--- assay method for ----------(b)(4)---------- ID for lot release purpose. -----(b)(4)------ assay is only being currently used for ongoing stability studies and will not be used in future for any -------(b)(4)------- drug product for lot release purposes.

2. ----------(B)(4)----------

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