DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food & Drug Administration
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To STN 125508/0

Through William M. McCormick, Ph.D., Director, OCBQ/DBSQC, HFM-680

Sponsor Merck and Co., Inc.

Product Human Papillomavirus 9-valent Vaccine, Recombinant, Gardasil®9; STN: 125508

Subject Primary Review Memo for ***Analytical Chemistry*** tests for the Drug Substances and Drug Product

Recommendation: Approval

Summary of Review

A new BLA was submitted for Human Papillomavirus 9-valent Vaccine, Recombinant, Gardasil®9; by Merck and Co., Inc., STN: 125508. This document constitutes the Primary Review Memo from DBSQC for the following analytical methods and their validations. These methods are used for lot release of the drug substance and the drug product.

Drug Substance

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

Drug Product

- Determination of Aluminum by ----------(b)(4)----------
- (b)(4)
- Characteristics by visual observation

Review of the methods and their validations led to two Information Requests (IR), which were submitted on 14 February 2014 and 25 April 2014. The responses were

received on 20 March 2014 (Amendment 5) and 8 May 2014 (Amendment 12), respectively. The responses are reviewed and included in this memo.

Conclusion: We found that the test methods mentioned above have been described and validated or qualified adequately and can be approved for lot-release.

Background of Submission

Merck and Co., Inc. submitted a new BLA for recombinant Human Papillomavirus 9-valent Vaccine (9vHPV); the proposed proprietary name is Gardasil®9. This 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, and is indicated for the prevention of different types of cancer, warts and lesion caused by these HPV Types. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. 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. 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 Chair of the review committee requested the Division of Biological Standards and Quality Control to review the lot-release tests for the final container product (DP) as well as the ----------(b)(4)---------- assays for the drug substance (DS) and the method validation for the same assays. This memo constitutes the Primary Review memo for the lot-release assays and their validations listed above under the Summary section, as performed by the DBSQC/LACBRP.

Submitted Information and Documents

This is an electronic submission. Information submitted and reviewed includes:

- 125508/0 – Cover letter, dated 10 Dec 2013
- 125508/0 – 3.2.S.4.1 Control of Drug Substance – Specification
- 125508/0 – 3.2.P.5.1 Control of Drug Product – Specification
- 125508/0 – 3.2.S.4.4 Batch Analyses
- 125508/0 – 3.2.P.5.4 Batch Analyses
- 125508/0 – 3.2.S.4.2.1 Analytical Procedure: ----------(b)(4)----------
- 125508/0 – 3.2.S.4.3.1 Validation of Analytical Procedures – ----------(b)(4)----------
- 125508/0 – 3.2.S.4.2.4 Analytical Procedures – Aluminum
- 125508/0 – 3.2.S.4.3.4 Validation of Analytical Procedures – Aluminum
- 125508/0 – 3.2.P.5.2.2 Analytical Procedures – Aluminum
- 125508/0 – 3.2.P.5.3.2 Validation of Analytical Procedures — Aluminum
- 125508/0 – 3.2.S.4.2.7 Analytical Procedure-(b)(4)
- 125508/0 – 3.2.S.4.3.8 Analytical Procedure-Characteristics
- 125508/0 – 3.2.S.4.3.7 Validation of Analytical procedure-(b)(4)
- 125508/0 – 3.2.S.4.3.8 Validation of Analytical procedure-Characteristics
- 125508/0 – 3.2.P.5.3.7 Validation of Analytical procedure-(b)(4)
- 125508/0 – 3.2.P.5.3.8 Validation of Analytical procedure-Characteristics

- 125508/0.4 – 1.11.1 Response to FDA information request dated 14 Feb 2014, Received on 14 March 2014
- 125508/0.5 – 1.11.1 Response to FDA information request dated 14 Feb 2014, Received on 20 March 2014
- 125508/0.12 – 1.11.1 Response to FDA information request dated 25 April 2014, Received on 08 May 2014
- Control procedure (CP 9110.699) – Aluminum Assay for Biologics, submitted to CBER in 2006 and referenced in the current submission

Review Narrative

1. Determination of ----------(b)(4)----------

The drug substance specification for the ---------(b)(4)---------- from each type.

Method

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

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

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

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First Information request: The following IR was submitted to the sponsor on 14 Feb 2014. The response by Merck Corp. received as Amendment 5 on 20 March 2014, is discussed below.

a. Please provide the detailed data for Qualification Parameters you summarized in Table 2 of section 3.2.S.4.3.1: Validation of Analytical Procedures – ----------(b)(4)---. Also, provide the composition of the diluent used in linearity and accuracy qualification studies you included in this table.

Response: The detailed data for the Qualification Parameters summarized in Table 2 of section 3.2.S.4.3.1 are provided below (*the sponsor included additional linearity and accuracy data*).

The composition of the diluent used in linearity and accuracy qualification studies included in this same Table 2 is ----------(b)(4)----------.

Please note that during the review of the detailed data for this response Merck discovered an error in some of the RSD values reported for Precision and Repeatability in Table 2 of section 3.2.S.4.3.1 (and subsequently in Table 9 of section 3.2.S.2.5.10). The error in the calculations was caused ----------(b)(4)----------. ….. After corrections, all RSD values still consistently meet the acceptance criteria of (b)(4). The original and new (corrected) summary values for Precision and Repeatability are presented in Table Q7-1 below for ease of comparison. All other validation criteria were unaffected by the error. All conclusions concerning the validation of the V503 ----------(b)(4)---------- Assay remain consistent and valid as submitted in the original dossier.

Review of response: Additional data for linearity, accuracy and precision were included in the IR response. The qualification data provided did not establish linearity and accuracy across the range of the procedure. Additional IR was submitted to the sponsor to address this issue.

Second Information request: Following the review of the response to 1st IR, an additional IR was submitted on 25 April 2014. The response by Merck Corp. received as Amendment 12 on 08 May 2014, is discussed below.

a. In your linearity study presented in Table Q7-6, you have presented slope of the ----------(b)(4)----------. However, no detail on the ----------(b)(4)---------- is provided. With the information you provided, it is not possible for us to assess if the linearity study covers the proposed range of the assay. Please provide data on the dilutions (range of concentrations) and data that were used to calculate the slope of standards and test samples corresponding to HPV types 31, 45, 52 and 58.

Response: In the linearity study presented in Table Q7-6, where the slope of the ------
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--(b)(4)---

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Review of response: As per the sponsor's response, test -(b)(4)- sample dilutions are in the range of the assay. However, the sponsor has not provided any data or explained as to how the assay range was established. Therefore, we do not think that the sponsor's response has adequately addressed this IR. However, the sponsor has submitted additional accuracy data of -------------------(b)(4)----------------- samples. We evaluated this data and found they demonstrated linearity of the assays in the stated working range. Therefore, no further IR is required.

b. In accuracy determinations shown in Table Q7-4, recovery of (b)(4) was studied using ---(b)(4)-- which do not cover the proposed range of the assay. Please provide data to demonstrate accuracy over the proposed range of the procedure.

Response: The accuracy determinations shown in Table Q7-4 represent the results for the sample qualification studies that were performed for ----------(b)(4)----------. For assay validation experiments the ----------
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----------(b)(4)----------

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Review of response: The accuracy determinations using ----------
----------(b)(4)----------

----------. The accuracy data is acceptable and the response by the sponsor is adequate.

Conclusion: The qualification report adequately demonstrates that the assay is suitable for its intended application.

2. Determination of Aluminum by ----------(b)(4)---------- Drug Product)

Aluminum is present in GARDASIL®9 as an adjuvant. Its concentration is determined and reported with specifications between ----------(b)(4)---------- based on Merck's experience with previous products and intermediates that include aluminum-based adjuvants. Control procedure, equivalent to an SOP, for the aluminum assay for biologics (CP 9110.699) was submitted to CBER in 2006.

Method

This method is used as a quantitative assay for measurement of the aluminum concentration in samples containing amorphous aluminum hydroxyphosphate sulfate adjuvant. The test article is ----------
---------(b)(4)----------

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

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

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Information Request

The following IR was submitted on 14 Feb 2014. The response by Merck Corp. received as Amendment 4 on 14 March 2014

a. Please provide the detailed data for Qualification Parameters you summarized in Table 1 of section 3.2.P.5.3.2: Validation of Analytical Procedures – Aluminum.

Response: The detailed data for the Qualification Parameters were summarized in Table 1 of section 3.2.P.5.3.2. Detailed data pertaining to accuracy, precision, specificity, linearity, and ruggedness were offered.

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

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

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ruggedness (intermediate precision) data submitted in the PedvaxHIB™ BLA is acceptable here as per an agreement between Merck and CBER.

Sponsor's response addressed the issue completely and is acceptable.

Conclusion: The assay is qualified for ----------(b)(4)---------- product HPV samples with Al concentrations between --------(b)(4)----------. The assay is (b)(4) qualified for determination of Al concentrations in ---------(b)(4)---------- samples.

3. Determination of ----------(b)(4)----------

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

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

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

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

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

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

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

4. Characteristics (---------(b)(4)-------- Drug Product)

The specification for the --------(b)(4)--------- final container product is white and cloudy liquid.

Method

Visual inspection is performed to check if the appearance of -------(b)(4)--------- final container product meets the specification. Since this method is simple visual inspection, validation was not performed, and this is acceptable.

Conclusion

The assay is approvable as a release test for HPV ----------(b)(4)-------- final container product.