



From: Alfred V. Del Grosso, Ph.D. OCBQ/DBSQC/LACBRP

Subject: MCM Vaccine (b) (4) (DTaP-IPV-Hib-HepB), Final Bulk Product Tests for (b) (4) Final Filled Product Tests for Physical Appearance, (b) (4), Aluminum and Extractable Volume.

To: File STN 125563/0

Through: Lokesh Bhattacharyya, Ph.D. OCBQ/DBSQC Chief LACBRP
William McCormick, Ph.D. OCBQ/ Director DBSQC

Recommendation: Approvable regarding the test methods evaluated by this reviewer.

Summary of Review

With the exception of the test for formaldehyde content in the final drug product, the physicochemical methods that are the subject of this review, (b) (4) aluminum, formaldehyde, (b) (4) physical appearance, (b) (4) and extractable volume have been evaluated as adequately described, appropriate for use and adequately validated with respect to the product specifications described in the original submission.

Regarding the test and specification for formaldehyde content, the sponsor had originally proposed the use of the (b) (4) method as a limits test with respect to a product specification of (b) (4). In response to a CBER information request, MCM agreed in Amendment 0.11, dated June 05, 2015, to establish a specification reflective of the capacity of the manufacturing process to remove formaldehyde and to implement the test as a quantitative assay procedure. The company proposed to revalidate the test with updated acceptance criterion by August 2016 as a post approval commitment. The sponsor's proposal is reviewed as satisfactory.

Background

MCM Vaccine Company (MCM), formed by Sanofi Pasteur SA (Sanofi) and Merck, Sharp and Dohme, Corp (Merck), submitted this BLA on 14 August, 2014 for a combined Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B

[Recombinant] Vaccine (DTaP-IPV-Hib-HepB), referred to as PR5I for product development purposes. The proposed trade name of this product is (b) (4)

PR5I is a hexavalent combination vaccine and supplied as a sterile fully liquid preservative-free, cloudy, white to off-white suspension presented as a single dose in a vial for intramuscular injection. PR5I is indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by *Haemophilus influenzae* type b (Hib) and infection caused by all known subtypes of hepatitis B virus in infants at 2, 4, and 6 months of age.

PR5I is manufactured using modified and /or existing bulk intermediates from vaccines already licensed in the United States by Sanofi and Merck.

Information Reviewed

This is an electronic submission. Information submitted and reviewed in support of this supplement included:

- 2.3.P.5 Control of Drug Product
- 3.2.P.5.1 Specifications
- 3.2.P.5.2 Analytical Procedures
 - (b) (4)
- 3.2.P.5.3 Validation of Analytical Procedures
 - (b) (4)
- Amendment 125563/0.10 – 05/28/15
 - 1.11.1 Quality Information Amendment 1
 - Q_0259174 (C013144), Validation report Addendum, “Measurement of Extractable Volume of PR5I vaccine 0.5 mL vials, final container mat# (b) (4) by (b) (4) Technique”
 - Q_0521595, Report for the Method Verification of (b) (4) Test for PR5I
 - Q_0521590, Report for the Method Verification of (b) (4) Determination for PR5I by Compendial Method Q_0515135
- Amendment 125563/0.11 – 06/05/15

Review Narrative

Test procedures that were evaluated in this review included (b) (4) Product Tests for (b) (4) Aluminum, Formaldehyde and (b) (4) and Final Filled Product Tests for Physical Appearance, (b) (4), Aluminum and Extractable Volume.

(b) (4)

[Redacted]

[Redacted]

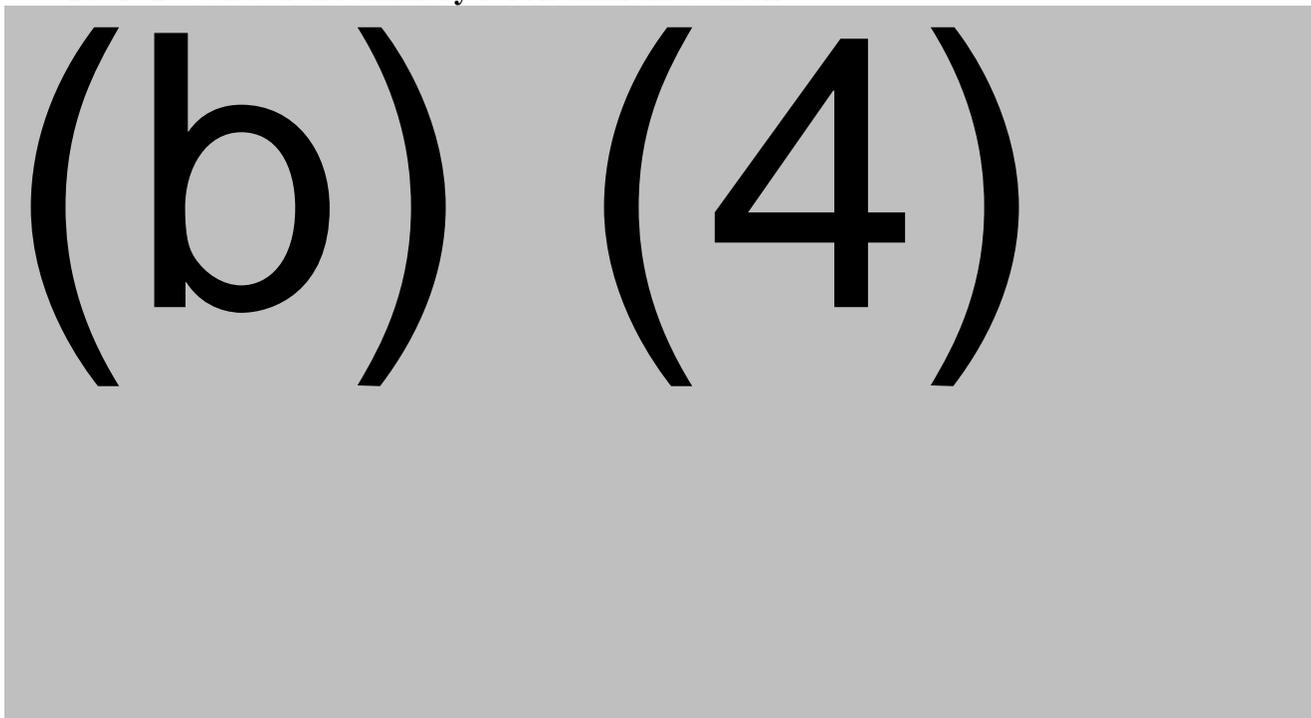
Aluminum Content

Aluminum content is determined in the (b) (4) Filled Product using a method according to (b) (4). The method is based on (b) (4)

[Redacted]

The proposed (b) (4) and filled product specification for aluminum is (b) (4). A summary of validation results, as extracted from the submission is listed in Table 1.

Table 1: Validation Summary for Aluminum Content

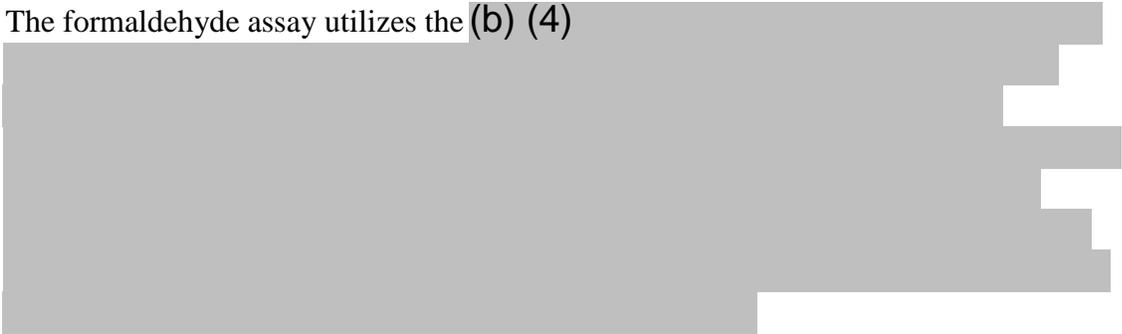


(b) (4)

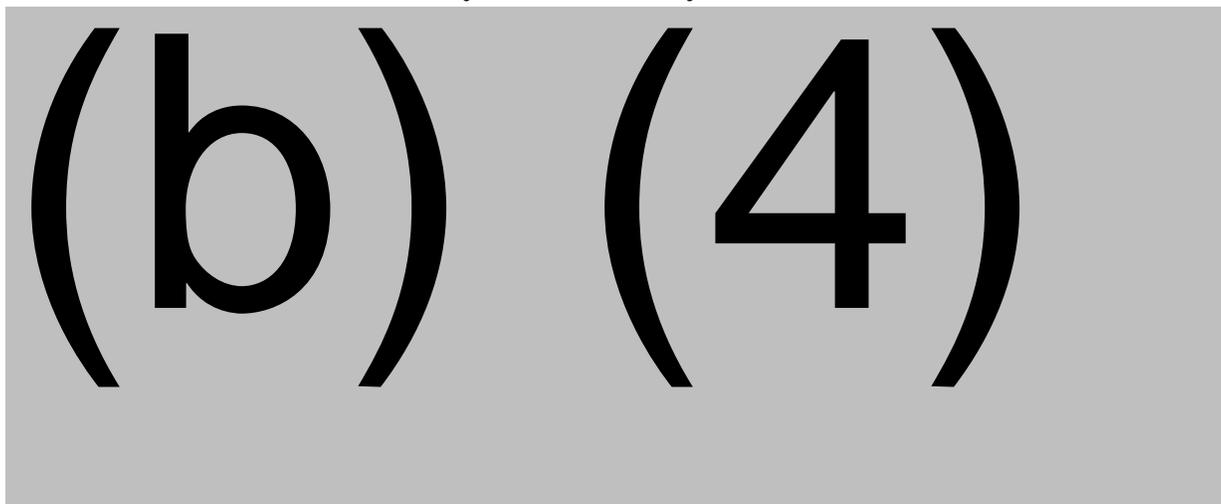
Reviewer's Evaluation: The procedure for aluminum was evaluated as appropriate for purpose as a component assay procedure. Validation studies were evaluated as adequate.

Formaldehyde Content

The formaldehyde assay utilizes the (b) (4)



As a limits test, the submitted validation addressed the characteristics of Specificity, Detection Limit and Robustness. Table 2 details the acceptance criteria and results as described in the original submission.

Table 2. Validation Summary for Formaldehyde

Reviewer’s Initial Evaluation: The reporting of formaldehyde as a limits test at a specification limit of (b) (4) was based on (b) (4), where it is stated that “(b) (4)”. In the opinion of this reviewer, it is appropriate for a significant impurity such as formaldehyde to be expressed as a quantitative result whenever practical and that specification limits be based on actual batch results. OVRP reviewers and the committee chair concurred with this assessment.

Information Request

As part of a CBER information request dated April 17, 2015, the following was requested of the sponsor.

3.2.P.5.2 Analytical Procedures - Formaldehyde Content – (b) (4) Product, **Item 20**. In section you state that “The result is reported as (b) (4) to the value defined as the specification limit.” In section 3.2.P.5.6 – Justification of Specifications, you state that “The acceptance criterion for the Formaldehyde Content Test (b) (4)) is based on the (b) (4)”. We request that you establish a specification reflective of the capacity of the manufacturing process to remove formaldehyde and that you report the actual results of the test in the certificates of analysis and lot release protocols for (b) (4) Product lots. As necessary, please modify this test method and validation to serve the purpose of a quantitative procedure.

Response: Received as part of Amendment 0.11, June 05, 2015.

The company agrees to comply with CBER’s request that a specification for the Formaldehyde test is established, which is reflective of the capacity of the manufacturing process to remove formaldehyde, and that the actual results of the test is reported in the certificate of analysis and the lot release protocol. In order to implement a quantitative Formaldehyde Content assay, the test method will need to be revalidated. The company proposes to complete the revalidation of

the test with an updated acceptance criterion as a post approval commitment. A supplement will be provided to CBER with the updated method by August 2016.

Reviewers evaluation: The sponsor's proposal to test residual formaldehyde as a quantitative assay procedure, to revalidate the method and to adopt a specification based on representative batch results is acceptable along with the proposed time frame.

(b) (4) [Redacted]

[Redacted]

[Redacted]

(b) (4)

(b) (4) [Redacted]

Physical Appearance – Filled Product

The physical appearance test is a qualitative determination by visual observation of the PR5I Filled Product. The sample is examined visually under normal laboratory light for clarity, color and presence of fibers and other impurities.

Validation was for the characteristic Specificity. (b) (4)

[Redacted]

Reviewer’s Evaluation: Appropriate for the intended use.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Extractable Volume – Filled Product

Test for extractable volume is intended to ensure that filled vials deliver the nominal volume of 0.5 mL indicated on the vial. Volume is calculated by dividing the (b) (4)

This test is performed according to (b) (4)

As a compendial method, a verification of suitability was conducted that evaluated the characteristics Accuracy, Precision and Ruggedness as a test for performance

characteristics. Reference was made to Verification Report Q_0259174. This report was submitted following a CBER request. This report made reference to a previous report for TDaP-IPV vaccine, 3VR-021. TDaP-IPV was described as having a (b) (4) identical to that of PR5I. It was the sponsor's conclusion that the extractable volume test method using (b) (4) technique is only related to the (b) (4) values and that verification by TDap-IPV is an acceptable demonstration that this technique is valid and suitable for measurement of extractable volume for PR5I.

Reviewer's Evaluation: Appropriate for the intended use.