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To	STN 125563/0 Amendments 32 and 41
Through	Lokesh Bhattacharyya, Chief, LACBRP, DBSQC/OCBQ
	Maryna Eichelberger, Director, DBSQC/OCBQ
Product	PR5I, (DTaP-IPV-Hib-HepB), (b) (4)
Sponsor	MCM Vaccine Company, Sanofi Pasteur SA and Merck Sharpe and Dohme.
Subject	(b) (4) Product Test for Formaldehyde

Recommendation: Approval

Summary: The modification of the test for residual formaldehyde in the PR5I (b) (4) to a quantitative procedure is acceptable along with the revised formaldehyde specification of (b) (4) . CBER's request made in the Information Request letter of 15 September 2015 has been satisfactorily addressed.

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 trade name of this product is (b) (4)   PR5I is manufactured using modified and /or existing bulk intermediates from vaccines already licensed in the United States by Sanofi and Merck. A Complete Response letter for this

product was issued on 01 November 2015. The decision to issue a CR letter was primarily based on issues related to potency and PRP-OMPC (b) (4) testing.

As part of the initial submission review, chemistry methods reviewed by DBSQC were found acceptable with the exception of the specification and limit test for residual formaldehyde in PR5I, and a PDR memo submitted on 26 June 2015. The following deficiency was included in an Information Request made by CBER dated 17 April 2015 as deficiency # 20:

> In section 3.2.P.5.2 Analytical Procedures - Formaldehyde Content – (b) (4) Product, 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.

In response to CBER's 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.

Amendment 0.32 was received on 04 April 2018. The sponsor submitted an updated release specification for PR5I Labeled Filled Product, a summary of the revised quantitative procedure for formaldehyde, a summary of the method validation, a justification for a revised formaldehyde specification and a representative COA for the (b) (4) Formaldehyde, (b) (4) used as a standard.

Information Reviewed

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

- Cover Letter – Amendment 32, 18Apr2018
- 1.11.1   Quality Information Amendment
- 3.2.P.5.1   Specifications
- 3.2.P.5.2   Analytical Procedures
- 3.2.P.5.3   Validation of Analytical Procedures
- 3.2.P.5.6   Justification of Specifications
- 3.2.P.6   Reference Standards or Materials
- Cover Letter – Amendment 21, 28Sep2018
- 1.1.1   Quality Information Amendment
- Q-0600205 Development Report for Modified Formaldehyde Determination Procedure SOP Q-0230801

- Q_0613802 Test Method Validation Report for Formaldehyde Determination by (b) (4) (b) (4) Method for PR5I
- Q_0612176 Test Method Validation Report for Procedure Q_0608752 Formaldehyde Determination by (b) (4) Method for (b) (4)

Review Narrative

The formaldehyde assay (b) (4)

As a quantitative procedure, the revised test method (SOP Q-0230801) is similar to the test being replaced with the exception that quantitation is performed against a (b) (4)

Assay validity criteria include that the correlation coefficient for the standards must be (b) (4) and that a separately prepared positive control solution must be determined as (b) (4)

The submitted validation study addressed the characteristics of accuracy, repeatability, intermediate precision, linearity, range, LOQ, specificity, and Robustness. These characteristics are recommended for a Quantitative Impurities Test in ICH-Q2(R1).

Accuracy was validated by (b) (4)

Repeatability was evaluated using (b) (4)

Linearity was assessed by (b) (4)

(b) (4)

Limit of Quantitation (LOQ) was defined as (b) (4)

Specificity was determined (b) (4)

Robustness was evaluated (b) (4)

The sponsor has proposed a revised specification for formaldehyde in PR5I product of (b) (4) This was based on (b) (4)

Results from (b) (4) batches of PR5I tested between July 2015 and March 2018 were trended and (b) (4) Determined values ranged from (b) (4) with an (b) (4) .

Initial evaluation and Information Request

In response to the evaluation of linearity described above, the following Information Request was made to the sponsor on 20 September 2018:

Question 1: Regarding 125563 Amendment 32, Section 3.2.P.5.3 – Validation of Analytical Procedures, Formaldehyde Content – (b) (4) Product:

In Section 2.3 "Linearity" is evaluated by (b) (4)

(b) (4)   . Please submit data to demonstrate linearity of analytical response against standard and sample concentrations.

Question 2: Please submit the cited validation reports Q_0612176, Q_0613802 and the development report Q_0600205.

A response was received on 28 September 2018. This was filed to the application as Amendment 41. Data demonstrating linearity of analytical response ((b) (4)   against concentration over the standard and spiked concentration ranges of (b) (4)   was presented along with graphs and regression calculations. Both sets of data demonstrated good linearity with (b) (4)   in both cases

Conclusion: The submitted procedure is adequately described and validated as a test for a quantitative impurity. The proposed specification of (b) (4)   is reasonable for a product of this type. It should be noted that this specification is a tightening of the previous proposed criterion of (b) (4)