



CBER REGULATORY REVIEW MEMORANDUM

Date 13 July 2015

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Office of Compliance and Biologics Quality (OCBQ)
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Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Number # 125510/0

Subject BLA: Review of Bioburden, Sterility and Endotoxin tests for FLUAD 65, Inactivated Influenza Virus Type A and B Hemagglutinin and Neuraminidase Vaccine, Adjuvanted

Through Dr. James L. Kenney, Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA
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Applicant Novartis Vaccines and Diagnostics (Novartis)

Product Inactivated Influenza Virus Type A and B Hemagglutinin and Neuraminidase Vaccine, Adjuvanted (FLUAD 65)

Biologics License Application (BLA) Submission Tracking Number (STN) 125510/0

Submission Received by CBER 25 November, 2014

Review Completed 13 July, 2015

Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) endotoxin tests performed on (b) (4) drug product for FLUAD 65, Inactivated Influenza Virus Type A and B Hemagglutinin and Neuraminidase Vaccine, Adjuvanted. In addition, information request responses received on 16 March, 17 April, 8 May, and 19 June of 2015 were also reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the bioburden, sterility and endotoxin test method were qualified in accordance with (b) (4) respectively, for FLUAD 65 and the product matrix is suitable for the intended test methods. In addition, the MF59C.1 adjuvant matrix was also shown to be suitable for their sterility test method.

Background

On 25 November, 2014, Novartis Vaccines and Diagnostics (Novartis) submitted a biologics license application for production of FLUAD 65, Inactivated Influenza Virus Type A and B Hemagglutinin and Neuraminidase Vaccine, Adjuvanted for active immunization of persons 65 years and older against influenza disease. The formulated vaccine would contain 45 µg HA per 0.5 mL dose in the recommended ratio of 15 µg HA each of the Influenza type A (H1N1), Influenza type A (H3N2) and Influenza type B and MF59C.1 (an oil-in-water emulsion) as an adjuvant.

The drug substance (DS) consists of three separate inactivated subunit influenza virus antigen concentrates, Monovalent Pooled Harvest (MPH) antigens and MF59C.1 adjuvant. The different MPH antigens are produced individually at Novartis' (b) (4) facility and the adjuvant is manufactured at their (b) (4) facility. For MPH antigen manufacturing, production eggs are inoculated with virus inoculum prepared from their working seed. (b) (4)

For MF59C.1 adjuvant manufacturing, emulsification is prepared using sodium citrate/citric acid buffer, polysorbate 80 and squalene in sorbitan trioleate. (b) (4)

The drug product (DP) is formulated at (b) (4) facility where MPH and MF59C.1 adjuvant are (b) (4) and final container product is tested for sterility (b) (4) and endotoxin (b) (4)

FLUAD 65 has been licensed outside of the United States under the label name of FLUAD. Since the manufacturing process is the same, the method qualifications have been performed on FLUAD and submitted for review.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are

released according to licensed test methods and product specifications. Therefore, this review will focus on the qualification of bioburden, sterility and endotoxin test performed on FLUAD, to indicate if the product matrixes are suitable for testing using the intended test methods.

Review

Bioburden Test Qualification for (b) (4) Antigens (b) (4) facility)

(b) (4)

The recovery of CFUs in the presence of (b) (4) antigens was greater than (b) (4) and did not differ by a factor greater than (b) (4) from the value of their respective positive control. All organisms showed comparable growth between the test sample and positive controls. The test was performed and compliant with (b) (4) and the more stringent test specifications were compliant with (b) (4) which indicated no inhibition of microorganism growth after the (b) (4) antigen was filtered.

Novartis submitted bioburden results of several (b) (4) antigens tested at (b) (4) facility from 2012 through 2015. The bioburden results showed (b) (4), which was within the proposed bioburden test specification (b) (4).

Sterility Test Qualification for MF59C.1 Adjuvant (b) (4) facility)

Novartis qualified MF59C.1 matrix using (b) (4)

(b) (4)

(b) (4)

. The test was performed and

compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism growth after the MF59C.1 adjuvant was filtered; thus indicating MF59C.1 adjuvant matrix is suitable for testing via their (b) (4) sterility test method.

Novartis performed sterility test on various lots of MF59C.1 manufactured from 2009 through 2015 using the (b) (4) method and all were reported to meet their specification of no growth.

Sterility Test Qualification for FLUAD DP Final Container (b) (4) facility)

Novartis qualified their FLUAD DP matrix using (b) (4) /media type of (b) (4) lots (i (b) (4)) using the same procedure and microorganisms as in the sterility test qualification for MF59C.1 adjuvant above. The test was performed and compliant with (b) (4) and the test results indicate there is no FLUAD DP inhibition on microorganism growth after filtration; thus indicating the FLUAD DP matrix is suitable for testing via their (b) (4) sterility test method.

Novartis performed sterility test on various lots of (b) (4) final containers of FLAUD vaccine using the (b) (4) method and all were reported to meet their specification of no growth.

(b) (4) Method Qualification (b) (4) Facility)

Novartis qualified their (b) (4)

(b) (4)

For DP, the test samples were tested at (b) (4), which showed no inhibition or enhancement as the spike recoveries for the PPC were between (b) (4) as calculated from the specification for DP's maximum endotoxin content (i.e., (b) (4)).

The routine testing of DP samples will be tested (b) (4). The bacterial endotoxin concentration results of (b) (4) for the test samples found during the inhibition/enhancement testing were well within their proposed alert limit of (b) (4) and their release specification of (b) (4).

All test results met their qualification acceptance criteria to qualify their matrixes for Novartis' (b) (4) method in accordance with (b) (4).

Conclusion

After a thorough review of the information submitted in this BLA, this reviewer finds Novartis' FLUAD 65 product matrix is suitable for testing using their sterility and endotoxin testing methods; these tests were qualified and performed in accordance with (b) (4) respectively. Furthermore,

the MF59C.1 adjuvant matrix was also shown to be suitable for their sterility test method. In addition, the (b) (4) matrix is suitable for testing using their bioburden and endotoxin testing methods and these qualifications were performed in accordance with (b) (4) respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.