

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125769/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Emnet Yitbarek, Ph.D.	Reviewer	5/26/2023		Kenneth Phillips Ph.D.	
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Jing Lin, Ph.D.	Reviewer	05/22/2023		Muhammad Shahabuddin, Ph.D.	
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Through Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ

Applicant: Pfizer Inc.

Subject: Review of Analytical Methods used for Lot Release of (b) (4) (b) (4) Drug Product.

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of ABRYSV0 (b) (4) DP and the associated method validations were reviewed:

1. Bioburden Test on (b) (4) (Claire H. Wernly)
2. Endotoxin test on (b) (4) (Claire H. Wernly)
3. Sterility Test on DP (Claire H. Wernly)
4. Endotoxin test on DP (Claire H. Wernly)
5. (b) (4) (Jing Lin)
6. Identity of (b) (4) DP by (b) (4) (Esmeralda Alvarado Facundo)
7. Relative Prefusion Content of (b) (4) DP by (b) (4) (Esmeralda Alvarado Facundo)

8. Host Cell Protein in (b) (4) by (b) (4) (Esmeralda Alvarado Facundo)
9. (b) (4) methods
 - a. Appearance (clarity) of reconstituted (b) (4) DP by (b) (4) (Emnet Yitbarek)
 - b. Appearance (coloration) of reconstituted (b) (4) DP by visual comparison (Emnet Yitbarek)

(b) (4)

 - i. Uniformity of Dosage Units of DP by (b) (4) (Emnet Yitbarek)
 - j. Residual moisture in DP by (b) (4) (Emnet Yitbarek)
10. Total protein concentration of (b) (4) (b) (4) DP by (b) (4) (Emnet Yitbarek)
11. (b) (4) in (b) (4) DP by (b) (4) (b) (4) (Emnet Yitbarek)
12. Purity of (b) (4) by (b) (4) (b) (4) (Emnet Yitbarek)
13. Residual Polysorbate 80 (PS80) in DP by (b) (4) (Emnet Yitbarek)
14. Physicochemical methods for the analysis of DP diluent water for injection (WFI) (Emnet Yitbarek)
15. (b) (4) Method for the Moisture Determination of DP (Hsiaoling Wang)

Conclusion: The analytical methods and their validations reviewed for the ABRYSV0 (b) (4) (b) (4) drug product were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original submission that describe control of (b) (4) DP (3.2.S.4, and 3.2.P.4), including descriptions of specifications, analytical procedures, and validation of these analytical procedures were reviewed. Additional information in amendments indicated by each reviewer were also reviewed.

Background

Pfizer submitted BLA 125769/0 on September 30, 2022 for ABRYSV0 (RSV preF Subunit Vaccine), a bivalent vaccine for Respiratory Syncytial Virus (RSV) containing stabilized prefusion F subunits. This vaccine is indicated for the prevention of (b) (4) and lower respiratory tract disease caused by RSV in individuals 60 years and older by active immunization. The two components of the DS, (b) (4) antigens, are manufactured separately using recombinant Chinese Hamster Ovary (CHO) cell lines that contain the DNA encoding the sequence for either one of the antigens. These antigens are trimeric, prefusion stabilized recombinant F glycoprotein ectodomains. The drug product is a sterile lyophilized powder with equal nominal amounts of the two stabilized drug substance antigens, (b) (4). The drug product is designed for delivery

of a 60 µg dose of each antigen, equivalent to a 120 µg dose of total protein. The lyophilized DP is supplied in a 2 mL clear glass vial, does not contain preservatives and is single use. Prior to use, the DP is reconstituted in the vial with a prefilled syringe containing sterile water diluent using a vial adapter. The entire content is withdrawn to enable a dose of 0.5 mL for intramuscular administration.

Sites where analytical methods were verified, qualified, validated or transfer are indicated below:

- (b) (4)
- Pfizer (b) (4)
- Pfizer (b) (4) in (b) (4)
- Pfizer (b) (4) in (b) (4)
- Pfizer (b) (4) in (b) (4)

Review

1. Bioburden Test on ^{(b) (4)} (Claire H. Wernly)

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

3. Sterility Test on DP (Claire H. Wernly)

Introduction

This test is performed on DP by Pfizer in (b) (4) Specification of 'No Growth Detected' must be met for the lot release of ABRYSV0 DP.

Method

The membrane filtration sterility test is used for filterable aqueous solutions in accordance with (b) (4) (b) (4) (b) (4)

The method is described in more detail below together with the tests that were performed to determine suitability of the test method for its intended use.

Method Qualification

(b) (4)

(b) (4)

Conclusion

The method suitability test was performed and compliant with (b) (4) and the test results indicate there is no product interference from the test sample, thus indicating the membrane filtration sterility test method is appropriate under the actual conditions of use for the DP at the Pfizer facility in (b) (4) (b) (4)

4. Endotoxin test on DP (Claire H. Wernly)

Introduction

This test is performed on DP at Pfizer (b) (4) in (b) (4) Specification of (b) (4) (b) (4) must be met for lot release of ABRYSV0 DP.

Method

(b) (4)

Method Qualification

(b) (4)

Conclusion

The method suitability tests were performed and compliant with (b) (4) and the test results indicate there is no product interference from ABRYVO DP test samples, thus indicating the (b) (4) test method is appropriate under the actual conditions of use.

(b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

6. Identity of (b) (4) DP by (b) (4) (Esmeralda Alvarado Facundo)

Introduction

The identity assay by (b) (4) identifies antigens (b) (4) in (b) (4) drug product. This method is a release test with a specification of "Positive"; the test is performed at Pfizer (b) (4) release testing, and (b) (4) (b) (4) for DP release testing.

(b) (4)

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(b) (4)

9.(b) (4) methods for:

a. Appearance (clarity) of (b) (4) DP (reconstituted) (Emnet Yitbarek)

Clarity testing for reconstituted (b) (4) DP is a qualitative test performed in accordance with (b) (4) and (b) (4) using (b) (4) method. The test is performed following an internal test method (TM) SOP-67108 v23. However, the TM for appearance, and (b) (4) other (b) (4) methods, were not provided with the original submission; hence, an information request (IR) was sent on December 5, 2022, for the sponsor to provide a Standard Operating Procedures (SOPs) or a detailed description and a verification report for this and the other (b) (4) methods stated below (#1-8). The sponsor replied with an amendment (STN125769/0/5) on December 19, 2022 and provided the method SOPs and their verification reports. The release specification for of DP/(b) (4) requires clarity to be (b) (4) (b) (4) and is reported as Yes or No compared to the clarity of a (b) (4) standard. The (b) (4) method was verified at Pfizer-(b) (4) (b) (4) using (b) (4) lot of DP, with (b) (4) measurements on each lot. The verification results show the system suitability of standards and DP release criteria were met (b) (4) test site. The method for (b) (4) was verified at (b) (4) however, verification report was not provided. Batch records of (b) (4)

(b) (4) and (b) (4) process lots show clarity of (b) (4) hence, Pfizer-(b) (4) (b) (4) (b) (4) is qualified for (b) (4) testing.

b. Appearance (coloration) of (b) (4) DP (reconstituted) (Emnet Yitbarek)

Coloration testing for reconstituted (b) (4) DP is a qualitative test performed in accordance with (b) (4) and (b) (4) by visual comparison to standard (b) (4) color reference solutions of varying intensity. The test is performed following an internal test method (TM) SOP-67108 v23. The release specification for DP/(b) (4) is that the sample cannot be more intensely colored than (b) (4) standard. The (b) (4) method was verified at Pfizer-(b) (4) using (b) (4) lot of DP, with (b) (4) measurements on each lot. The verification results show the system suitability of standards and the DP release criteria were met at (b) (4) test site. The method for (b) (4) was verified at (b) (4) however, verification report was not provided. Batch records of (b) (4) and twelve (b) (4) (b) (4) process lots met the (b) (4) release criteria; hence, Pfizer-(b) (4) is qualified for (b) (4) testing.

(b) (4)

(b) (4)

i. Dosage (content) uniformity of DP (Emnet Yitbarek)

Content uniformity is performed to determine dose consistency of DP vials by (b) (4) in accordance with (b) (4). The test is performed following an internal test method (TM) SOP-114874 v3. The total protein concentration of DP is used to calculate the percent of label claim and the latter is then used, in combination with the value of DP (b) (4) to determine the Uniformity of Dosage Units in DP vials. The DP acceptance criteria are that the release results must meet (b) (4) requirements set for solutions of freeze-dried drugs in final containers (b) (4). The method was verified at Pfizer-^{(b) (4)} using ^{(b) (4)} lots of DP with (b) (4) measurements on each lot. The results show all system suitability and (b) (4) release criteria were met.

j. Residual moisture of DP (Emnet Yitbarek)

Residual moisture testing is performed on the lyophilized DP in accordance with (b) (4) (b) (4). The method is a quantitative test for the determination of residual moisture using (b) (4) it provides a means to evaluate the effectiveness of the lyophilization process. An information request (IR) was sent on December 5, 2022, for the sponsor to provide an SOP or a detailed description of the moisture method, and a full validation report. The sponsor replied with an amendment (STN125769/0/5) on December 19, 2022 and provided the method SOP and the full validation report.


(b) (4)

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10. Total protein concentration of (b) (4) DP (Emnet Yitbarek)

Introduction


The purpose of this analytical procedure is to quantify the total protein concentration of RSV DP (b) (4) samples by (b) (4). The RSV vaccine consists of two antigens (b) (4) in a single 120 µg dose vial reconstituted with a prefilled syringe of sterile water for intramuscular injection. The (b) (4) are trimeric, prefusion stabilized recombinant F glycoproteins composed of (b) (4). Total protein concentration is determined using (b) (4).



An information request (IR) was sent on December 5, 2022, for the sponsor to provide an SOP or a detailed description of the total protein method. The sponsor replied with an amendment (STN125769/0/5) on December 19, 2022 and provided the method SOP.

Method

(b) (4)



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(b) (4)

13. Quantitation of Polysorbate 80 in RSV DP samples by (b) (4)

(b) (4) with (b) (4) (Emnet Yitbarek)

Introduction

The purpose of this analytical procedure (SOP-114868v4) is to quantify Polysorbate 80 (PS80) concentration in DP samples by (b) (4). PS80 is a synthetic nonionic surfactant which is often added to stabilize protein drug formulations, and its detection requires a universal detector, like (b) (4) since PS80 structure lacks strong chromophore that precludes readily available UV and fluorescence detectors. PS80 concentration in DP needs to be monitored closely during DP release and long-term stability study. Generally, (b) (4)

An information request (IR) was sent on December 5, 2022, for the sponsor to provide an SOP or a detailed description of the PS80 method. The sponsor replied with an amendment (STN125769/0/5) on December 19, 2022 and provided the method SOP.

Method

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

14. (b) (4) methods for the analysis of diluent water for injection (WFI) (Emnet Yitbarek)

Introduction

Sterile water diluent (WFI) is used to reconstitute lyophilized DP to obtain the final RSVpreF vaccine. The diluent is supplied at (b) (4) target fill volume in a 1 mL glass prefilled syringe (PFS) syringe with Luer lock adapter, plunger and a covered tip cap. There is an excess of (b) (4) to ensure the required volume (b) (4) is available to reconstitute the vaccine. The WFI in PFS undergoes terminal sterilization and visual inspection prior to packaging with the lyophilized DP. After the lyophilized drug product is reconstituted, at least (b) (4) volume of injection (VOI) is required during administration to a patient. The sponsor performed a confirmatory study to demonstrate at least (b) (4) can be delivered in a worst-case scenario when reconstitution is performed using a drug product vial and diluent PFS filled at their respective lower reject limits. Hence, the combination drug product design ensures that the intended dose of at least 0.5 mL at a concentration of (b) (4) (b) (4) is delivered when the entire contents are extracted and injected.

(b) (4) define WFI as the only compendial water used as an excipient for parenteral solutions. Hence, analytical methods used for testing WFI quality attributes, shown in Table1, were based on (b) (4)

(b) (4) monographs. The manufacturing and release testing of the WFI product for STN25769 was performed at the Pfizer-(b) (4) (Pfizer Manufacturing in (b) (4)) and all the methods (Table1: #1-15), except the container closure integrity (CCI) testing, are performed for releasing the WFI product. CCI testing is only performed during annual stability time point.

Verification of the compendial methods (Table 3: 1-15) was successfully completed at Pfizer-(b) (4) site; additionally, full verification studies of the endotoxin and sterility assays were successfully completed, and the corresponding verification reports were submitted with the file, STN125769/0 (section 3.2.P.5.3).

(b) (4)

A validation of the container closure integrity (CCI) by (b) (4) was performed at Pfizer-(b) (4) and Pfizer-(b) (4) correspondingly, the validation results are reported in documents 20080-CCITS-MVRA-A1 and RPT-29400 respectively. During CCI testing, the closure of the diluent/drug product container is evaluated to verify that the sterility of the product can be guaranteed. Container closure failures can be detected when a (b) (4) into the syringes. The validation was performed according to protocol 20080-CCITS-MVP0-A1 and the validation characteristics that were evaluated include:

- Attributable Agreement Analysis
- Probability of Misclassification
- (b) (4) visual detection limit

The validation result shows all acceptance criteria of the characteristics above were met; hence, the CC method was demonstrated to be appropriate for testing CCI of PFS and Pfizer-(b) (4) is qualified to perform the method.

Conclusion

All test methods used for releasing WFI product were adequately verified (or validated) for their intended purpose at the Pfizer-(b) (4) site and are suitable for their intended purposes.

15. (b) (4) Method for the Moisture Determination of DP (Hsiaoling Wang)

Review Narrative

The residual moisture is currently determined by (b) (4) method for the lyophilized DP with specification of (b) (4). The firm plans to use (b) (4) method as an alternative method for moisture determination. The comparability protocol and preliminary results were provided in 3.2.R.1. of initial submission.

The comparability protocol of (b) (4) method is not acceptable because it is not designed to include sufficient DP batches and spectra to establish a robust (b) (4) model for DP moisture determination. In addition, the specificity evaluation in the preliminary validation report was not challenged by negative samples.

The review committee sent out an information request on May 12, 2023 to ask the firm to withdraw this document from the BLA and recommended that (b) (4) assay SOP, validation protocol and validation report or comparability protocol be submitted as a prior approval supplement (PAS) after approval of the BLA. The firm withdrew the document in Amendment 64.