

**DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO**

**To:** STN 125740/0

**From:** CBER/OCBQ/DBSQC reviewers listed in the table below

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Hsiaoling Wang	Lead Reviewer	06/15/2021		Kori Francis	
Simleen Kaur	Reviewer	07/06/2021		James Kenney	
Anil Choudhary	Reviewer	07/22/2021		Muhammad Shahabuddin	

**Through:** Maryna Eichelberger, Ph.D., Division Director, CBER/OCBQ/DBSQC

**Applicant:** Pfizer Inc.

**Subject:** Review of Analytical Methods used for the lot release of TicoVac (b) (4) Drug Product

**Recommendation:** Approval

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## I. Review Summary

The following analytical methods used for lot release of TicoVac (b) (4) Drug Product and their associated validations or qualifications, were reviewed:

1. Bioburden (Simleen Kaur)
2. Sterility (Simleen Kaur)
3. Bacterial Endotoxin (Simleen Kaur)
4. Determination of Total Protein Content (Hsiaoling Wang)
5. (b) (4) Formaldehyde (Hsiaoling Wang)
6. Sucrose Content (Hsiaoling Wang)
7. Protein Content (Hsiaoling Wang)
8. Sodium Content (Hsiaoling Wang)
9. Aluminum Content (Hsiaoling Wang)
10. General (b) (4) Methods: (b) (4) extractable volume, and visual inspection (Hsiaoling Wang)
11. Antigen Content (b) (4) (Anil Choudhary)
12. Identity Test (b) (4) (Anil Choudhary)
13. Antigen Content (b) (4) (Anil Choudhary)
14. In vivo Potency assay (Anil Choudhary)
15. Identity (b) (4) (Anil Choudhary)

## Conclusion

The analytical methods and their validations and/or qualifications reviewed for the TicoVac (b) (4) drug product were found to be adequate for their intended use.

## II. Documents Reviewed

Information in sections of the original submission that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP, specifications of DS and DP, analytical procedures of DS and DP, validation of analytical procedures, and batch analyses of DS and DP. Reference standards or materials of DS and DP in sections 3.2.S.5 and 3.2.P.5 were also reviewed. Additional information in amendments specified in the content were reviewed by each reviewer.

## III. Background of the Submission

On December 15, 2020, Pfizer submitted this Biologics License Application (BLA) for approval of TicoVac, intended for active immunization to prevent Tick-Borne Encephalitis (TBE) in individuals 1

year of age and older through intramuscular injection. This vaccine is also known as FSME-IMMUN and has received marketing authorization in 32 countries including in the European Union and elsewhere. Pfizer acquired the vaccine from Baxter and the marketing authorizations were transferred from Baxter to Pfizer in 2015.

TicoVac is a sterile, non-pyrogenic suspension of formaldehyde-inactivated and sucrose gradient purified TBE virus harvest, diluted in phosphate buffered saline solution containing 0.1% human albumin and bound to aluminum hydroxide. The DP is presented as a single use pre-filled syringe (PFS) available in two dosage forms, 0.5 mL PFS for adults and 0.25 mL PFS for children.

DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriately described, validated and suitable for their intended purpose. The tests are validated for use with specific material; the terminology for DS and DP materials include:

- (b) (4)
- DP (b) (4)
- Final (b) (4) Vaccine: (b) (4)
- Final DP: Filled Syringe

#### IV. Review Narrative

##### 1. Bioburden (Simleen Kaur)

###### Method

(b) (4)

###### Method Qualification

(b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

**Information Request and Review**

The following questions were sent in an IR to the sponsor on January 8 and February 18, 2021 and responses were received on January 28, March 5, and June 25, 2021, respectively.

(b) (4)

[Redacted]

- b. Please provide the procedure used for product specific validation study including (b) (4)

[Redacted]

Review of the Response

Pfizer submitted explanation of missing evaluation of (b) (4)

[Redacted]. Based on the response, a follow up IR question was sent.

- c. Your information request response received January 29, 2021, has been reviewed and CBER does not agree with replacing evaluation of (b) (4)

[REDACTED]

Please provide the assessment protocol and complete results so CBER can ensure the validation was performed in accordance with (b) (4) [REDACTED]. Otherwise, CBER requests (b) (4) [REDACTED] be reevaluated in accordance with (b) (4) [REDACTED] and submitted for continued review.

Review of the Response

Pfizer acknowledged CBER's request and committed to reevaluate (b) (4) [REDACTED]

[REDACTED] A requalification report was submitted 25 June 2021 and results were found acceptable.

**2. Sterility (Simleen Kaur)**

**Method**

(b) (4) [REDACTED]

**Method Qualification**

(b) (4) [REDACTED]

[REDACTED]

(b) (4)

[Redacted]

[Redacted]

**Information Request and Review**

The following question was sent in an IR to the sponsor on January 8, 2021 and response was received on January 28, 2021.

(b) (4) [Redacted] Please submit the missing information for continued review.

Review of the Response

Pfizer submitted detailed qualification reports for (b) (4) [Redacted] methods that included all the missing information. The response was found acceptable.

**3. Bacterial Endotoxin (Simleen Kaur)**

**Method**

(b) (4) [Redacted]

(b) (4)

### Method Qualification

The original submission did not include detailed qualification reports for (b) (4). Therefore, an IR was sent on January 8, 2021, requesting the complete qualification reports. Based on the response received, a follow-up IR was submitted on February 18, 2021. The description of the qualifications that follows takes into consideration the response to the IRs.

(b) (4)

### Information Request and Review

The following questions were sent in an IR to the sponsor on January 8, February 18 and March 17, 2021 and responses were received on January 28, March 5, and March 26, 2021, respectively.

- a. Please provide a detailed bacterial endotoxin qualification reports for (b) (4). The reports should include (b) (4) and (b) (4).

Review of the Response

Pfizer submitted detailed qualification reports for (b) (4). Upon review of the qualification reports, a follow up IR question was sent.

- b. According to method verification report for bacterial endotoxin- (b) (4), (b) (4) can be found in attachment 3 of the report. However, no attachments were provided for the report. Please submit attachment 3 of the document to ensure the chosen (b) (4).

Review of the Response

Pfizer submitted detailed information on preliminary investigation of selected (b) (4). Even though selected (b) (4) was found acceptable, it was noted that formula used in calculation of (b) (4) was incorrect. Therefore, another IR was sent.

- c. Based on preliminary testing results submitted for bacterial endotoxin testing, CBER finds the selected sample testing (b) (4) acceptable for testing the (b) (4). However, the calculation for (b) (4) is incorrect. (b) (4) is calculated by (b) (4).

(b) (4)

CBER requests the (b) (4) be corrected in Table 1 of the IR response to 18 February 2021 FDA Information Request as well as method verification report for bacterial endotoxin- (b) (4) and submitted to CBER for continued review.

Review of the Response

Pfizer submitted an explanation of (b) (4) calculation and response was found acceptable.

**4. Determination of Total Protein Content (Hsiaoling Wang)**

(b) (4)

(b) (4)

**Method**

(b) (4)

[Redacted text block]

**Method Validation**

(b) (4)

[Redacted text block]

(b) (4)

(b) (4)

### Information Request and Review of the Response

Following IRs were sent to the firm after initial review on March 24, 2021:

A. Please provide a SOP or an in-depth description of this analytical method with following details:

- Determination of the specific (b) (4)
- Acceptance criteria of the control
- Description of the (b) (4)

B. Regarding the validation of this method:

- 1) Please provide a validation report or a detailed description of the validation study with results and acceptance criteria.
- 2) Please provide the description for the (b) (4) mentioned in the 3.2.S.4.3.5 - Specificity. The assay range was (b) (4) from the summary of validation while the stated applicable range in the method description is (b) (4); please provide justification for this inconsistency.
- 3) The assay range was (b) (4) from the summary of validation while the stated applicable range in the method description is (b) (4) please provide justification for this inconsistency.
- 4) You acknowledge the accuracy of the method was not validated due to lack of (b) (4). However, for a quantitative assay, it is critical to demonstrate accuracy under actual conditions of use as specified in CFR211.194 (2). Please provide data to demonstrate accuracy of your assay. We recommend evaluation of accuracy by (b) (4)

The responses were received on April 7, 2021 in the amendment 9.

### Review of the responses

- A. An English translation of SOP from German was provided by the firm. In the translated SOP, the (b) (4) [REDACTED]. A follow-up IR was sent to the firm.
- B. The firm provided an updated validation report (RTP-112607 version 1.0). It included detailed description of the validation study and results with acceptance criteria. The (b) (4) [REDACTED]. The responses to 1), 2), and 3) were satisfactory. But the accuracy study did not exist. A follow-up IR was sent to the firm.

The 2nd IRs for this assay were sent to the firm on April 30.

- A. The translated SOP of "Determination of Total Protein Content" for (b) (4) you provided to FDA question (Q) #1a has the specific (b) (4) in section 6.9.1 without mentioning how it was established. This value should be determined based on protein content obtained from a validated or an (b) (4) method. Please provide details of how this critical value is determined.
- B. There is no accuracy evaluation in your updated validation report (RPT-112607) for "Determination of Total Protein Content" for (b) (4). Accuracy can be inferred from (b) (4). You did not provide any data from a (b) (4) study. Please note that a (b) (4) used in this method is generally considered non-specific. As we recommended in the IR dated March 24, 2021, please provide accuracy results from a (b) (4). Alternatively, you may demonstrate accuracy of the total protein method by comparing results obtained from an (b) (4) method (Q #1b 4)).

The responses were received on May 14, 2021 in the amendment 15.

Review of the responses

- A. (b) (4) [REDACTED]. The approach is acceptable.
- B. (b) (4) [REDACTED]. The response is acceptable.

Based on the information provided by the original BLA and amendments, the method has been validated for its intended purpose.

**5. (b) (4) Formaldehyde (Hsiaoling Wang)**

Formaldehyde is used to inactivate the TBE virus during the manufacturing procedure (b) (4) [REDACTED]

(b) (4)

**Method**

(b) (4)

[Redacted]

**Method Validation**

(b) (4)

[Redacted]

(b) (4)

(b) (4)

(b) (4)

### Information Request and Review of the Response

Following IRs were sent to the firm after initial review on March 24, 2021:

- A. You stated that (b) (4) formaldehyde is determined for (b) (4) final DP in 3.2.P.5.2 “ANALYTICAL PROCEDURES – (b) (4) FORMALDEHYDE CONTENT”. However, there is no specification of (b) (4) formaldehyde in 3.2.P.5.1 “SPECIFICATIONS” for final DP. Validation report (RPT-106046) does not contain results from any final DP sample. If the test is performed for the final DP, please provide the specification and validation data.
- B. The method of determination of (b) (4) formaldehyde content was validated in your quality control laboratory in (b) (4). If the method is used by laboratories other than this site, please submit method transfer report.

- C. (b) (4) [redacted] Please provide details of sample preparation or document PLAN-8396.

The responses were received on April 7, 2021 in the amendment 9.

Review of the responses

- A. The firm clarified that (b) (4) formaldehyde is determined (b) (4) [redacted]. The section 3.2.P.5.2 Analytical procedures has been corrected. The response is acceptable.
- B. The firm stated that formaldehyde method is only used by quality control laboratory in Pfizer, (b) (4) [redacted]. The response is satisfactory.
- C. The firm stated that samples (b) (4) [redacted]. The samples are acceptable to be used for the validation study.

Based on the information provided by the original BLA and amendment, the method has been validated for its intended purpose.

**6. Sucrose Content (Hsiaoling Wang)**

(b) (4) [redacted]

**Method**

(b) (4) [redacted]

(b) (4) [redacted]

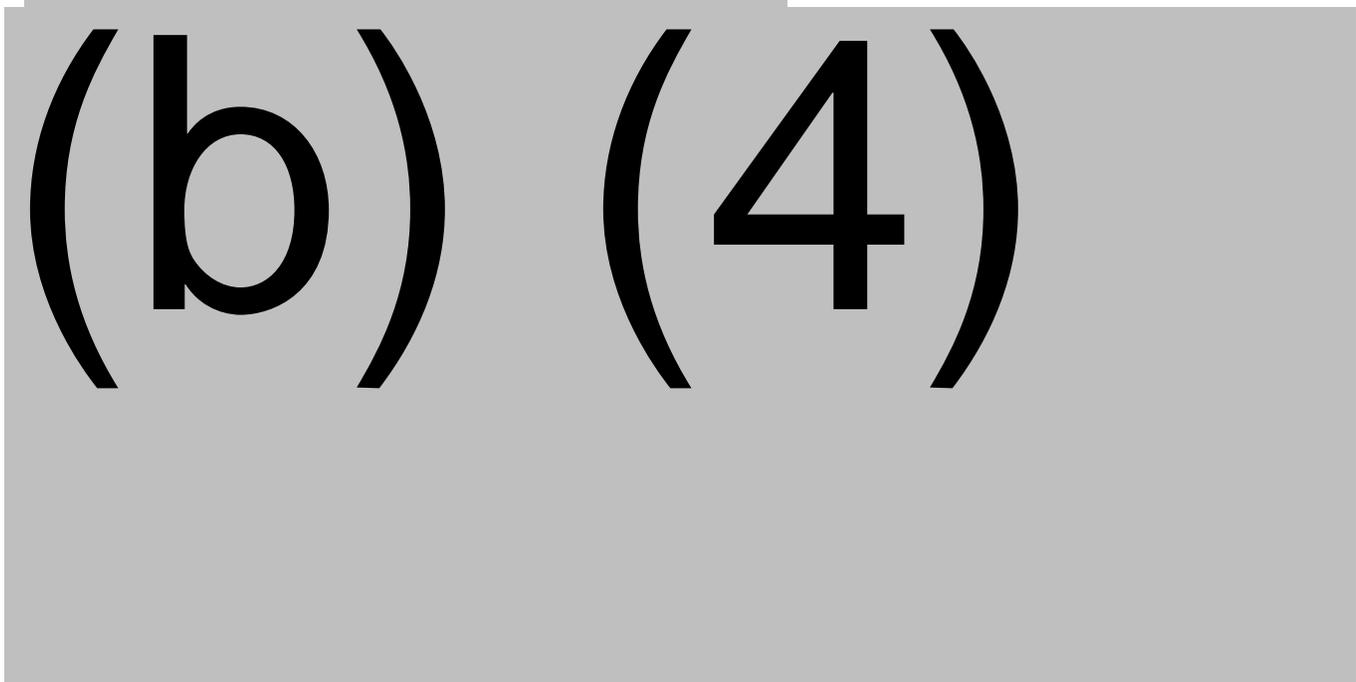
(b) (4) [redacted]

(b) (4)



**Method Validation**

(b) (4)



**(b) (4)**

(b) (4)

(b) (4)

(b) (4)

**Information Request and Review of the Response**

Following IRs were sent to the firm after initial review on March 24, 2021:

A. Please provide the following details for this analytical method (CD-86356):

- (b) (4)

B. Regarding the validation of this method (RPT-105859):

- 1) Please provide details of sample (b) (4) from the TicoVac (b) (4)

- 2) Your pre-defined acceptance criterion for accuracy (b) (4) did not meet the set limits. Please provide an explanation for large variation of (b) (4) and explain why the accuracy results are acceptable.
- 3) Please provide details of the deviation mentioned in Section 4.4.

The responses were received on April 7, 2021 in the amendment 9.

#### Review of the responses

- A. The firm clarified that TicoVac (b) (4) in section 6.6.1 were also provided to have adequate description of the (b) (4). The response is satisfactory.
- B. The firm stated in the response as reviewed below:
  - 1) (b) (4)  
These sample are acceptable for validation use.
  - 2) The defined acceptance criterion was set for the (b) (4) rather than individual value. Due to inherent method variation, it was expected that individual value could fall outside the stringent acceptance criterion.
  - 3) The details of the deviation were provided and has been incorporated in the validation section of this method.The responses are acceptable.

Based on the information provided by the original BLA and amendment, the method has been validated for its intended purpose.

#### **7. Protein Content (Hsiaoling Wang)**

(b) (4)

#### **Method**

(b) (4)

(b) (4)

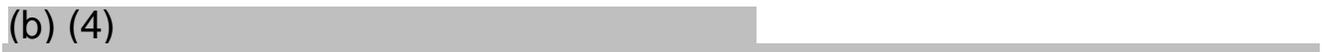
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**Method Validation**

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

### Method Transfer

(b) (4)

### Information Request and Review of the Response

Following IRs were sent to the firm after initial review on March 24, 2021:

A. Please provide the following details for this analytical method (TM-01-7097A-06):

- (b) (4)

B. Regarding the validation of this method (VN1104026TB-CVRX1.02):

(b) (4)

The responses were received on April 7, 2021 in the amendment 9.

### Review of the responses

A. The firm stated that the (b) (4) or equivalent was used for the (b) (4). However, the critical parameters for (b) (4) and (b) (4) were not provided. A follow-up IR was sent to the firm in the second IR.

(b) (4)

(b) (4) and established limits were acceptable.

B. The explanations provided by the firm as reviewed below are acceptable:

- 1) The firm stated that human serum albumin (b) (4) Using human serum albumin (b) (4) A follow-up IR was sent to the firm to confirm the suitability for the intended TicoVac (b) (4)
- 2) The requested (b) (4) results for the accuracy study were provided and are incorporated in the validation summary above.

The 2nd IRs for this assay were sent to the firm on April 30, 2021.

- A. Please provide operational parameters of (b) (4) method of "Protein Content" for Drug Product (DP) (b) (4) (Q #4a).
- B. Because of the similarity between TicoVac (b) (4)

The responses were received on May 14, 2021 in the amendment 15.

#### Review of the responses

- A. The stated that the (b) (4) is carried out under (b) (4). The response is satisfactory.
- B. The (b) (4) precision data were provided for the TicoVac (b) (4) The results demonstrated that the method is accurate and precise enough for the intended use.

Based on the information provided by the original BLA and amendments, the method has been validated for its intended purpose.

### **8. Sodium Content for DP (Hsiaoling Wang)**

(b) (4)

#### **Method**

(b) (4)

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(b) (4)

### Information Request and Review of the Response

Following IRs were sent to the firm after initial review on March 24, 2021:

- A. Please provide the following details for this analytical method (TM-01-7096A-04):
  - Description of the (b) (4) and its qualification
  - The acceptance criteria for (b) (4)
- B. Regarding the validation of this method (VN1104082TB-CVRX2.01):
  - 1) Please provide (b) (4) data for samples prepared in TicoVac (b) (4) or explain why the (b) (4) results for accuracy evaluation using (b) (4) are appropriate for validation of this method to measuring sodium content of TicoVac (b) (4)
  - 2) Regarding the method transfer:  
Please provide reproducibility results with pre-defined acceptance criterion for transferring the method from Pfizer, (b) (4)

The responses were received on April 7, 2021 in the amendment 9.

### Review of the responses

- A. The firm stated that the commercially available human serum is used as the (b) (4)

The responses are acceptable.

- B. The explanations provided by the firm as reviewed below are acceptable:
  - 1) (b) (4)

Based on the information provided by the original BLA and amendment, the method has been validated for its intended purpose.

### 9. Aluminum Content for DP (Hsiaoling Wang)

Aluminum hydroxide is used as adjuvant for the vaccine. Aluminum content is determined by (b) (4)

**Method**

(b) (4)

(b) (4)

(b) (4)

**Method Validation**

(b) (4)

(b) (4)

Summary of Results for Aluminum Content (b) (4)

(b) (4)

**Method Transfer**

(b) (4)

(b) (4)

### Information Request and Review of the Response

Following IR was sent to the firm after initial review on March 24, 2021:

Please provide a description of the control and its acceptance criteria for the method of "Aluminum Content" (TM-0107045A-05) for (b) (4) test.

The response was received on April 7, 2021 in the amendment 9.

#### Review of the responses

A TicoVac DP (b) (4) is used as the (b) (4). The established limits of (b) (4) . The response is acceptable.

Based on the information provided by the original BLA and amendment, the method has been validated for its intended purpose.

### 10. General (b) (4) Methods for DP (Hsiaoling Wang)

There are four (b) (4) methods used for DP analysis as shown in the table below.

(b) (4)

These methods do not require validation.

(b) (4)

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(b) (4)

The response is satisfactory

### Visual Inspection

The visual inspection is performed according to (b) (4) for TicoVac final DP. Each filled syringe was inspected visually (b) (4).

Method qualification is described as technical report (FORM-48049) with (b) (4) lots of representative final DP in 0.25 mL and 0.50 mL syringes in (b) (4). The outcomes were both described as (b) (4), the vaccine is an off-white, opalescent suspension, no extraneous matters”, which met the proposed specification of final DP.

Based on the information provided by the original BLA and amendment, these four methods have been verified for their intended purposes.

### 11. Antigen Content by (b) (4) (Anil Choudhary)

#### Method

(b) (4)

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(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

**12. Identity (b) (4)**

[Redacted text block]

[Redacted text block]

[Redacted text block]

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

13. Antigen Content (b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

**14. *In Vivo* Potency Assay (Anil Choudhary)**

(b) (4)

[Redacted text block]

[Redacted text block]

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

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**15. Identity Test by (b) (4) (Anil Choudhary)**

The purpose of this analytical method is to determine the identity of drug product in the final container. The assay is performed at (b) (4) facility. The Sponsor provided (b) (4) test methods in the submission: (b) (4)

[Redacted]

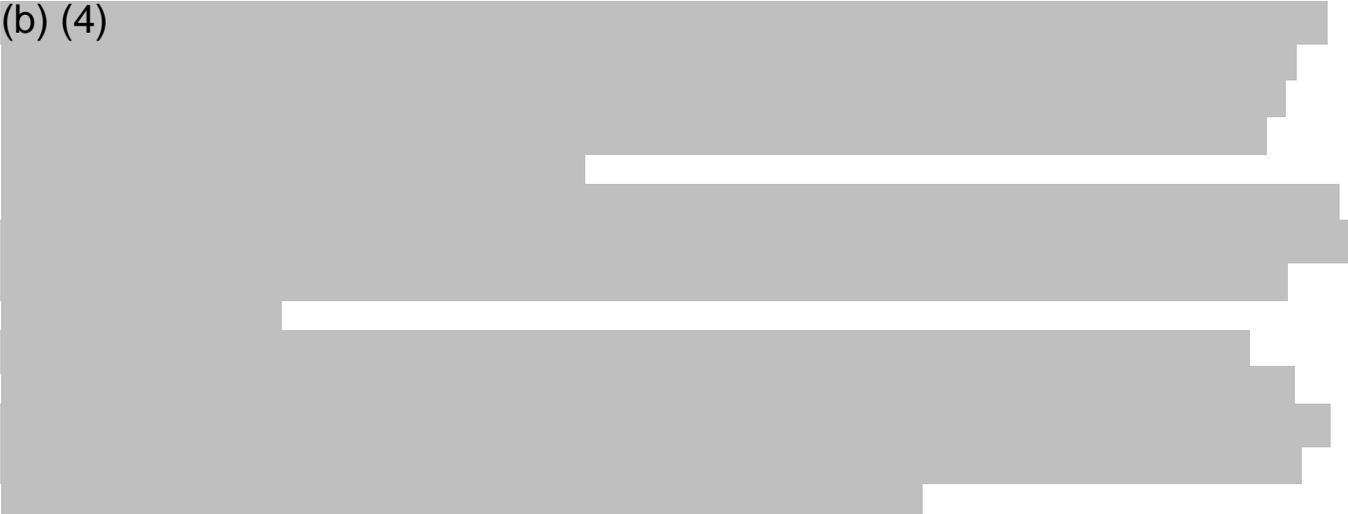
**Method**

(b) (4) [Redacted]

[Redacted]

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

(b) (4)



### **Conclusion**

The analytical procedure for determination of identity (b) (4) in DP by (b) (4) met all the predefined acceptance criteria and therefore, the assays are suitable for their intended purposes. Although the data support the use of (b) (4) to (b) (4), this test is not used to release DP.