



**DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO**

**To:** The file STN 125776

**From:**

Reviewer	Role	Date finalized	Stamp	Laboratory/Lab Chief	Stamp
Parmesh Dutt, Ph.D.	Reviewer	07-14-2023		Kori M Francis	
Hyesuk Kong, Ph.D.	Reviewer	01-06-2023		Simleen Kaur, M.S. (Acting)	
Emnet Yitbarek	Reviewer	07-24-2023		Kenneth S. Phillips, Ph.D.	

**Through** Maryna Eichelberger, Ph.D.  
Division Director, DBSQC

**Applicant:** Octapharma

**Subject:** Analytical Methods used for BALFAXAR (Octaplex), Prothrombin Complex Concentrate [Human] Drug Substance and Drug Product

**Recommendation:** Approval

**Summary:**

The following analytical methods used for lot release of BALFAXAR (Octaplex) drug substance (DS) and Drug Product (DP), and the associated reports for assay validations/qualifications were reviewed:

1. FIX (b) (4) Assay (Parmesh Dutt)
2. (b) (4) test for DS (Hyesuk Kong)
3. Sterility test for DP (Hyesuk Kong)
4. Endotoxin test for DP (Hyesuk Kong)
5. (b) (4) methods:
  - a. Appearance of (b) (4) /DP (Emnet Yitbarek)
  - b. (b) (4) DP (Emnet Yitbarek)
  - c. (b) (4) of DP (Emnet Yitbarek)
  - d. Residual moisture of DP (Emnet Yitbarek)
6. (b) (4) of DP (Emnet Yitbarek)

7. (b) (4) in DP (Emnet Yitbarek)
8. (b) (4) in DP (Emnet Yitbarek)
9. Determination of Citrate in DP (Emnet Yitbarek)
10. Physicochemical methods (b) (4) for the analysis of DP diluent water for injection (WFI) (Emnet Yitbarek)

**Conclusion:** The analytical methods and their validations and/or qualifications reviewed for BALFAXAR (Octaplex) drug substance and drug product were found to be adequate for their intended use.

**Documents Reviewed:**

Information in sections of the original submission that describe control of DS and DP (2.2, 2.3, 3.2.S.4, 3.2.P.5, and 3.2.R respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validations of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

**Background:**

Octapharma submitted a Biological License Application for BALFAXAR (Octaplex, Prothrombin Complex Concentrate (Human). BALFAXAR is a human plasma-derived prothrombin complex concentrate containing the coagulation factors II, VII, IX and X and Proteins C and S. BALFAXAR is supplied as a lyophilized powder for reconstitution for intravenous use. The diluent for reconstitution of the lyophilized powder is Water for Injection. Octaplex is standardized according to the factor IX content. It is available with a nominal strength of 500 IU in 20 mL reconstitution volume and 1000 IU in 40 mL reconstitution volume per vial. BALFAXAR is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with (b) (4) need for an urgent surgery or invasive procedure.

**Review Narrative:**

**1. FIX (b) (4) Assay**

Introduction:

The FIX specification for the (b) (4) is (b) (4) with confidence limits of (b) (4) of the estimated potency.

(b) (4)

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(b) (4)

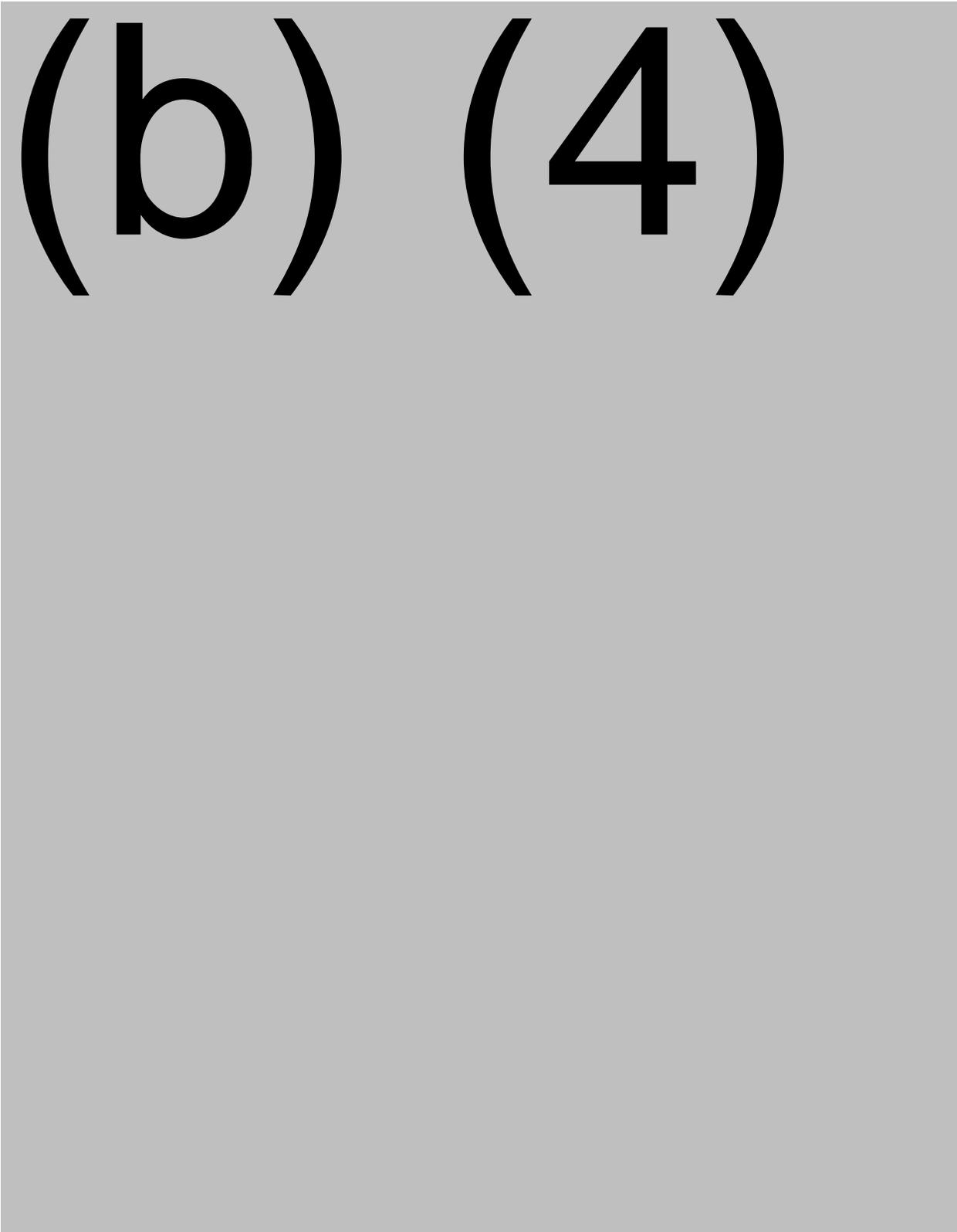
Conclusion

The FIX activity assay was appropriately validated for its intended purpose at both the QC laboratories in (b) (4) (b) (4) main validation site) and Vienna (OPG). The method is suitable for testing FIX activity in (b) (4) DP samples of BALFAXAR.

2. (b) (4) Method for DS

Method:

(b) (4)



(b) (4)

**3. Sterility Test for Drug Product**

Method

(b) (4)

Sterility Test Qualification

(b) (4)

Conclusion

The method suitability test was performed and compliant with (b) (4) and the test results indicate there is no product inhibition of microorganism growth, thus indicating

the (b) (4) sterility test method is appropriate under the actual conditions of use.

#### 4. Endotoxin test for DP

##### Method

(b) (4)

##### (b) (4)-BET Qualification

(b) (4)

(b) (4)

### Conclusion

The method suitability test was performed and compliant with (b) (4) the test results indicate there is no interference from Octaplex DP test samples, thus indicating the (b) (4) BET test method is suitable under the actual conditions of use.

### 5. (b) (4) methods

a. Appearance (b) (4) DP  
Appearance testing for (b) (4) lyophilized DP powder is a qualitative test performed by visual inspection following an internal test method (TM) 130SOP006, "Visual inspection of freeze-dried products, (b) (4) (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products". The TM is based on (b) (4) and covers appearance release testing for (b) (4) DP samples. The visual inspection is performed to check if the appearance of the products complies with the respective specifications and to verify the complete solubility of the freeze-dried final product according to (b) (4) The appearance release specifications are the following:

- (b) (4)
- The lyophilized DP is a white to ice-blue powder or friable mass, very hygroscopic
- The lyophilized DP dissolves completely in 20 mL (500 IU) and 40mL (1000IU) WFI within (b) (4) at 20-25°C, giving a clear solution that may be colored.

The sponsor did not provide the method verification data for TM 130SOP006, hence an IR was sent on June 05, 2023. The sponsor responded on 13 Jun, 2023, with an amendment STN125760/0/40. In the response, the sponsor explained verification is waived according to (b) (4) since appearance is a (b) (4) procedure and they routinely perform the assay on similar licensed plasma protein products; hence the analysts are extensively trained performing the assay. The response provided is satisfactory and accepted.

Batch analysis on (b) (4) DP lots shows appearance testing results comply with the specification and the solubility times were (b) (4) There was no batch analysis data for (b) (4) appearance.

b. (b) (4)

(b) (4)

c (b) (4)

(b) (4)

d. Moisture of DP (unreconstituted)

Residual moisture of the lyophilized DP is determined by (b) (4) (b) (4) methods. Both methods were fully validated using the same set of test samples. The (b) (4) tests are performed at

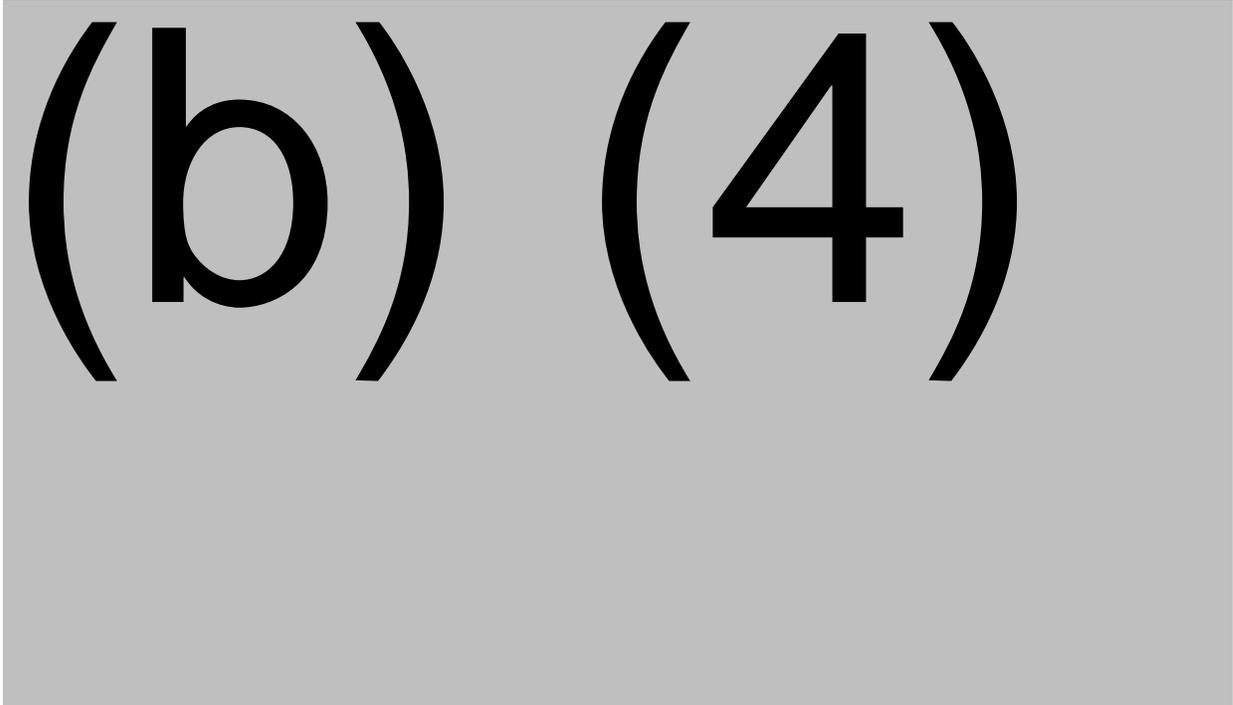
OCTAPHARMA QC Labs in Vienna, Austria; the DP specification for residual moisture measured by either assay is (b) (4)

- i. Moisture of DP by (b) (4)

Introduction

The method is a quantitative test for the determination of residual moisture using (b) (4) (b) (4) is determined (b) (4). The method is performed in accordance with (b) (4)

Method



Method validation



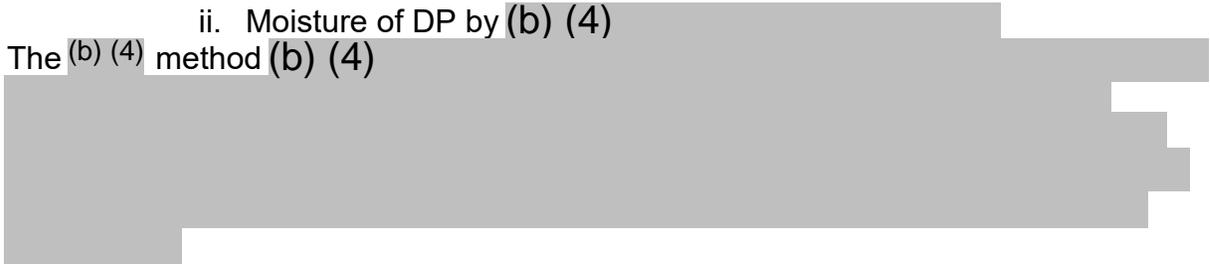
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Conclusion

Residual moisture determination by (b) (4) method was validated for its intended purpose at OCTAPHARMA QC Labs in Vienna, Austria; hence, the method is demonstrated to be suitable for the determination residual moisture in DP samples.

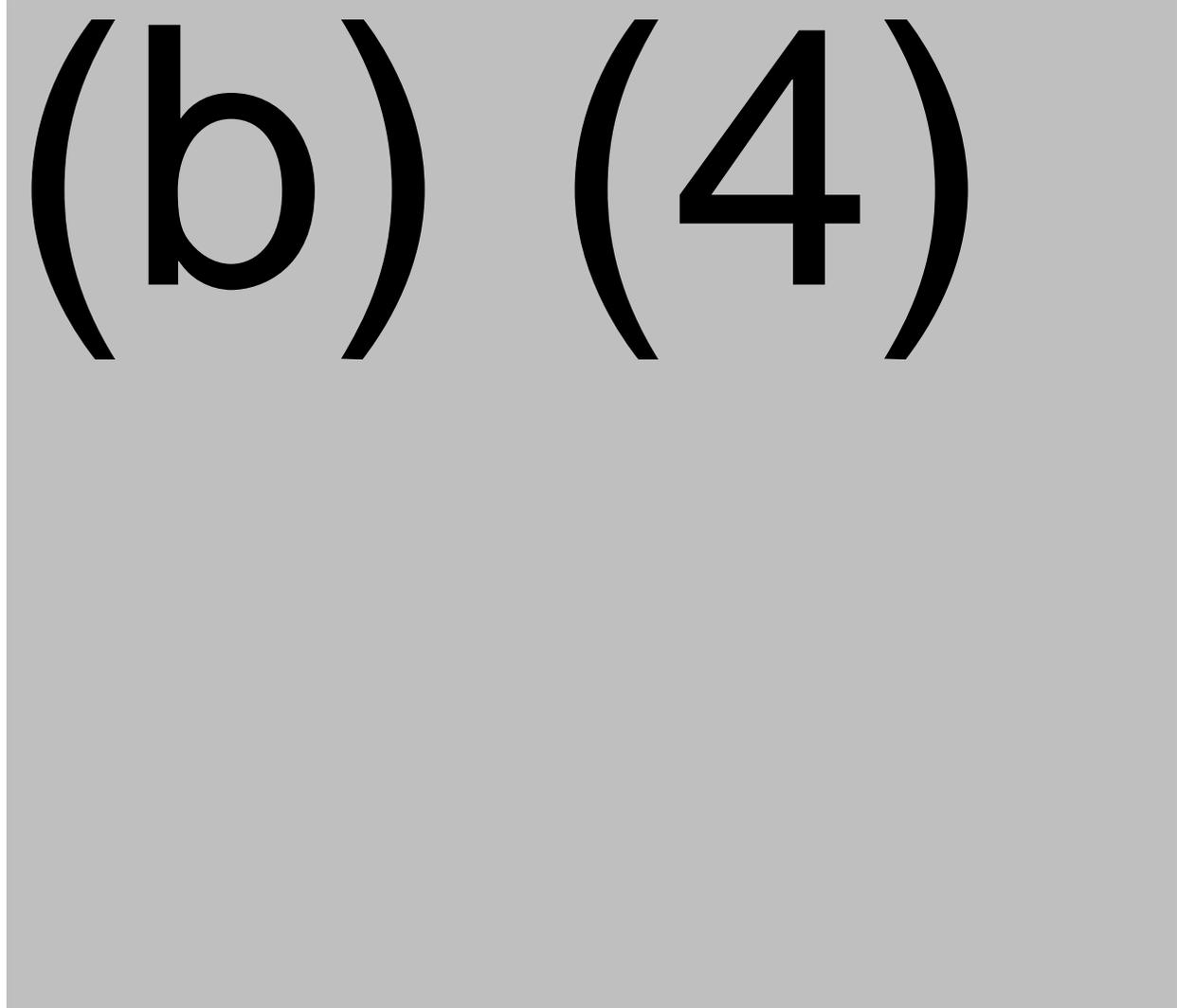
ii. Moisture of DP by (b) (4)

The (b) (4) method (b) (4)



Method

(b) (4)



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(b) (4)

Conclusion

Residual moisture determination by (b) (4) was validated for its intended purpose at OCTAPHARMA QC Labs in Vienna, Austria; hence, the method is demonstrated to be suitable for the determination of residual moisture in DP samples.

**6. (b) (4) (b) (4) and reconstituted DP**

Introduction

The (b) (4) method is used to quantify the (b) (4) in (b) (4) reconstituted DP sample by (b) (4). The (b) (4) method is a (b) (4) (b) (4)

The (b) (4) method is performed according to (b) (4). The (b) (4) (b) (4) specification for (b) (4) DP are (b) (4)

Method

(b) (4)

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(b) (4)

#### Conclusion

(b) (4) determination by (b) (4) method was validated for its intended purpose at OCTAPHARMA QC Labs in Vienna, Austria; hence, the method was demonstrated to be suitable for determination of (b) (4) in (b) (4) DP samples.

#### 7. Determination of (b) (4) in DP

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(b) (4)

8. Determination of (b) (4)

in DP

(b) (4)

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(b) (4)

**9. Determination of Citrate in OCTAPLEX® Final Product Samples by (b) (4) according to (b) (4)**

Introduction

Citrate is present in the lyophilized final DP at a concentration of 16.8 – 23.4 mmol/L to maintain (b) (4) when the DP is reconstituted with WFI (water for injection) prior to administration. The amount of citrate in the reconstituted DP is determined using (b) (4) (b) (4) with (b) (4) (b) (4) set at (b) (4). This method is based on a (b) (4) method used for the determination of citrate in (b) (4) final product samples by (b) (4) and concentration is determined using a (b) (4) (b) (4)

Method

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(b) (4)

Conclusion

Citrate determination method by (b) (4) was appropriately validated for its intended purpose at OCTAPHARMA QC Labs in Vienna, Austria; hence, the method is demonstrated to be suitable for quantitation of citrate in Balfaxar DP samples.

**10. (b) (4) methods for the analysis of diluent water for injection (WFI)**

Introduction

The sterile water diluent (WFI) is designed to reconstitute lyophilized DP and is supplied in 20 and 40mL (b) (4) colorless glass vials with bromobutyl rubber stoppers and sealed with a flip off cap.

The WFI undergoes (b) (4) sterilization and visual inspection prior to packaging with the lyophilized DP.

The WFI is manufactured and supplied to the sponsor (Octapharma) by (b) (4) (b) (4) located in (b) (4) (b) (4) and all testing is carried out by (b) (4) except for sterility testing which is performed by a contract testing facility (b) (4) (b) (4) (b) (4)

Hence, quality attributes used for testing are shown in Table 3 and are based on (b) (4) (b) (4)

Table 1. Quality attributes and acceptance for Sterile Water (WFI) Diluent

#	Quality attribute	Test Procedure	(b) (4) specification Limit	Test result (?)
1	Appearance	(b) (4)	Clear, colorless solution, essentially free of visible particles	Pass
2	Particulate Contamination / Sub-visible Particulates	(b) (4)	(b) (4)	Pass
3	(b) (4)	(b) (4)	(b) (4)	Pass

4	(b) (4)	(b) (4)		Pass		
5	(b) (4)			Pass		
6	(b) (4)			Pass		
7	(b) (4)			Pass		
8	(b) (4)			Pass		
9	(b) (4)			Pass		
10	(b) (4)			Pass		
11	(b) (4)			Pass		
12	(b) (4)			Pass		
13	Extractable volume			Extractable volume, (b) (4)	20mL: (b) (4) 40mL: (b) (4)	Pass
14	Endotoxin			Endotoxin (b) (4) (b) (4)	(b) (4)	Pass
15	Sterility			Sterility, (b) (4)	No growth detected	Pass

Conclusion

The sponsor did not provide method verification data for WFI product, however the batch analyses results of (b) (4) lots (20 mL and 40mL) indicate the (b) (4) limits were met for the WFI product.