



## MEMORANDUM

**From** Hsiaoling Wang, DBSQC/OCBQ  
Tao Pan, DBSQC/OCBQ  
Noel Baichoo, DBSQC/OCBQ  
Ritu Agarwal, DBSQC/OCBQ  
Grainne Tobin, DBSQC/OCBQ  
Mark Levi, DBSQC/OCBQ  
Lokesh Bhattacharyya, DBSQC/OCBQ

**To** STN 125555/0

**Through** Dr. William M. McCormick, Director OCBQ/DBSQC

**Sponsor** Octapharma

**Product** Antihemophilic Factor (Recombinant) – rAHF, B-domain deleted recombinant Factor VIII – BDDrVIII, plasma/albumin free (Nuwiq®)

**Subject** Primary Review Memo for the Method Validation for the Quality Control Release Tests for the Drug Product, STN: 125555

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### Summary

A new BLA was submitted by Octapharma for Nuwiq, an Antihemophilic Factor (Recombinant) – rAHF, B-domain deleted recombinant Factor VIII (BDDrVIII) plasma/albumin free product for the prevention and control of bleeding episodes (also during and after surgery) in adults and children with Hemophilia A. This document constitutes the Primary Review Memo from DBSQC for the following analytical methods and their validations, which are used for quality control lot release of the drug product.

1. One-stage Factor VIII Clotting Assay
2. Identification by (b) (4)
3. (b) (4)
4. Total Protein by (b) (4)
5. Water by (b) (4)

6. Arginine by (b) (4)
7. Sucrose by (b) (4)
8. Poloxamer 188 Content by (b) (4)
9. Sodium Content by (b) (4)
10. Chloride by (b) (4)
11. Citrate by (b) (4)
12. Calcium by (b) (4)
13. Appearance (Lyo Cake) by Visual Inspection, Solubility of freeze-dried final products, and Visual inspection of solutions Solubility and Visual Inspection of solution
14. (b) (4)
15. (b) (4)

Review of the methods and their validations led to two Information Requests (IR), which were submitted on 22 August and 17 October 2014. The sponsor provided responses to the IRs on 2 September, 10 October, and 30 October, 2014 as Amendments 4, 7, and 9, respectively.

#### Conclusion:

There are outstanding method validation related issues for the following tests:

- (b) (4)
- Sucrose by (b) (4)
- Calcium by (b) (4)

IRs were sent to the sponsor, requesting them to provide information to address the issues. The evaluation of sponsor's responses to assess adequacy of these three tests will be reported in the addendum memo. All other tests listed above have been validated adequately and are suitable for lot-release testing of the drug product.

#### **Background**

The B-domain deleted recombinant Antihemophilic Factor (factor VIII) (BDDrVIII) is a plasma/albumin free product that is supplied as lyophilized powder. Recombinant Antihemophilic Factor VIII (rAHF) is comprised of light and heavy chain complexes.

(b) (4)

The lyophilized powder is formulated in single-dose vials containing 250 IU, 500 IU 1000 IU or 2000 IU recombinant factor VIII per vial, which is reconstituted as a single-dose with 2.5 mL of sterile water for injection before use from a pre-filled syringe supplied with the product.

#### **Submitted Information and Documents**

This is an electronic submission. Information submitted and reviewed includes:

- 125555/0.0 – 3.2.P.5.1 Control of Drug Product – Final Product Specification
- 125555/0.0 – 3.2.P.5.2 Control of Drug Product – Analytical Procedures

- Doc. 130SOP730/00: One Stage FVIII:C assay on (b) (4)
- Doc. 130SOP723/00: (b) (4)
- Doc. 130SOP735/04: (b) (4) for analysis of Human cell line recombinant human factor VIII
- Doc. 130SOP740/02: Determination of protein concentration of Human-cl rhFVIII by (b) (4)
- Doc. 130SOP714/01: (b) (4) water determination according to (b) (4)
- Doc. 130SOP131/06: Determination of Chloride by (b) (4)
- Doc. 130SOP032/03: Determination of Citrate with (b) (4)
- Doc. 130SOP160/02: Determination of L-Arginine and L-Lysine using a (b) (4)
- Doc. 130SOP168 versions 03/04: Determination of Sucrose by (b) (4)
- Doc. 130SOP716/01: Quantitative determination of Poloxamer 188 with (b) (4)
- Doc. 130SOP 029/03: Determination of Sodium and Potassium by (b) (4)
- Doc. 130SOP131/06: Determination of Chloride by (b) (4)
- Doc. 130SOP032/03: Determination of Citrate with (b) (4)
- Doc. 130SOP708 versions 04/05: Determination of calcium content by (b) (4)
- Doc. 130SOP006/04: Visual inspection of freeze-dried products, (b) (4) and (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products
- Doc. 130SOP028/03: Determination of (b) (4)
- Doc. 130SOP008/02: Determination of the (b) (4)
- 125555/0.0 – 3.2.P.5.3 Control of Drug Product – Validation of Analytic Procedures
  - Doc. 138VAL730 IP 13 FC 137 FC 139/01: Report of the Method Validation for the Determination of Coagulation Factor VIII in Human-cl rh FVIII IP (b) (4) Drug Product by One Stage Factor VIII:C assay on (b) (4)
  - Doc. 138VAL730 IP 13 FC 137 FC 139/02: Report of the Method Validation for the Determination of Coagulation Factor VIII in Human-cl rh FVIII IP (b) (4) Drug Product by One Stage Factor VIII:C assay on (b) (4)
  - Doc. 138VAL723 FC 137 FC 139/02: Validation Report for (b) (4) and Drug Product of Human-cl rhFVIII
  - Doc. 138VAL735 IP 137, FC 139/03: Validation Report for Determination of (b) (4) DP of Human-cl rhFVIII by (b) (4)
  - Doc. 138VAL740 IP FC 137 FC 139/01: Determination of the protein concentration in (b) (4) drug product of Human-cl rhFVIII by (b) (4)

- Doc. 138VAL714 FC 139/01: (b) (4) determination of water acc. (b) (4) in drug product of Human-cl rhFVIII
- Doc. 138VAL131 FC 139/02: Validation Report of Determination of Chloride by (b) (4) in Drug Product of Human-cl rhFVIII
- Doc. 138VAL032 FC 139/01: Validation Report of Determination of Citrate with (b) (4) in Drug product of Human-cl rhFVIII
- Doc. 130SOP006/04: Visual inspection of freeze-dried products, drug substance and (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products
- Doc. 138VAL168 FC 139 versions 01/02: Validation of the method used for the Determination of Sucrose
- Doc. 138VAL716 FC 139/02: Validation Report for the Determination of Poloxamer 188 by (b) (4) in Drug Product of Human-cl rhFVIII
- Doc. 138VAL029 FC 139/01: Validation Report for the Quantitative determination of Sodium in Drug Product of Human-cl rhFVIII, acc. (b) (4).
- Doc. 138VAL131 FC 139/02: Validation Report of Determination of Chloride by (b) (4) in Drug Product of Human-cl rhFVIII
- Doc. 138VAL032 FC 139/01: Validation Report of Determination of Citrate with (b) (4) in Drug product of Human-cl rhFVIII
- Doc. 138VAL708 FC 139 versions 01/02: Validation of the method used for the Determination of Calcium content
- Doc. 130SOP006/04: Visual inspection of freeze-dried products, drug substance and (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products
- Doc. 138VAL028 FC 139/01: Validation Report for Determination of (b) (4) in Drug product of Human-cl rhFVIII acc. (b) (4)
- Doc. 138VAL008 FC 139/00: Validation Report for Determination of the (b) (4) in Human-cl rhFVIII for clinical trials by the (b) (4)
- 125555/0.0 – 3.2.P.5.4 Batch Analyses
- 125555/0.4 – 1.2 Cover Letters: Response to FDA information request dated 22 August 2014; response received on 2 September 2014
  - Doc. 130SOP131/07: Determination of Chloride by (b) (4)
  - Doc. 130SOP032/04: Determination of Citrate with (b) (4)
  - Doc. 138VAL032 FC 139/02: Validation Report of Determination of Citrate with (b) (4) in Drug product of Human-cl rhFVIII
- 125555/0.7 – 1.2 Cover Letters: Response to FDA information request dated 22 August 2014 response received on 10 October 2014
  - Doc. 130SOP735/05: (b) (4) for analysis of Human cell line recombinant human factor VIII
  - Doc. 138VAL735 IP 137, FC 139/05: Validation Report of Determination of (b) (4) DP of Human-cl rhFVIII by (b) (4)
  - Doc. 138VAL714 FC 139/02: (b) (4) determination of water acc. (b) (4) in drug product of Human-cl rhFVIII

- Doc. 138VAL160 FC 139/02: Determination of L-Arginine in Human-cl rhFVIII drug products using a (b) (4)
- 125555/0.9 – Response to FDA Information Request, received 30 October, 2014
- Doc. 138VAL730 IP 13 FC 137 FC 139/02: Analytical Method Validation Report – Report of the Method Validation for the Determination of Coagulation Factor VIII in Human-cl rh FVIII IP (b) (4) Drug Product by One Stage Factor VIII:C assay on (b) (4)

## Review Narrative

### 1. One-stage Factor VIII Clotting Assay

This method is a one stage clotting factor assay used to measure the FVIII potency in human-cl rhFVIII [Antihemophilic Factor (Recombinant)] Intermediate Product (IP) sample 13, the (b) (4) and the drug product. Four different potencies of the drug product are available, 250 IU, 500 IU, 1000 IU and 2000 IU/vial. The specifications for Human-cl rhFVIII drug product are (b) (4), respectively. The sponsor provided a Standard Operation Procedure, SOP 130SOP730/00, as well as a validation report, 138VAL730 IP 13 FC 137 FC 139/01.

#### Method

The assay is based on the ability of a FVIII sample to correct the prolonged coagulation time of FVIII-deficient plasma. The sample is (b) (4)

The potency of the sample is determined by comparison of linear plots of serial dilutions of sample to standard curves and is expressed in International Units. A house standard calibrated against the WHO International Concentrate Standard, 07/350, is used together with a house control sample. Standards and samples are (b) (4)


. The method is clearly described in the SOP, 130SOP730/00. Each standard (b) (4) Acceptance criteria for the assay included the following: (b) (4)

#### Method Validation

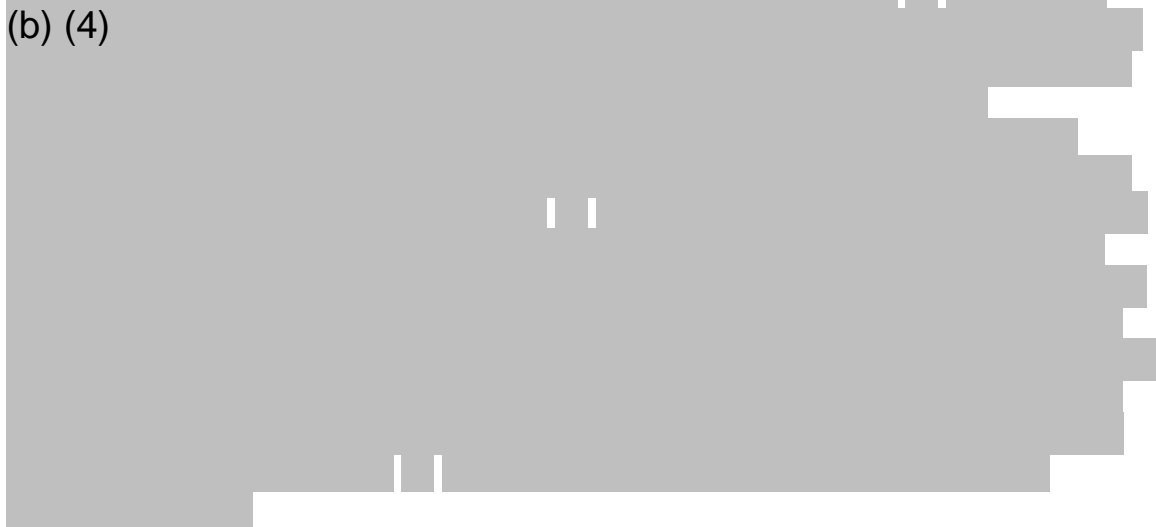
This is a quantitative method and is validated according to ICH guidelines. The Analytical Method Validation Report, 138VAL730 IP 13 FC 137 FC 139/01, contained

evaluation of the following validation characteristics: specificity, sensitivity, accuracy, repeatability, intermediate precision, linearity and range, quantitation limit and robustness. The validation was carried out in the Octapharma facility in (b) (4).


(b) (4)




(b) (4)



(b) (4)



(b) (4)



(b) (4)

(b) (4)

(b) (4)

#### Information Request and Review

The following IR was submitted to the sponsor on 10/16/2014. The response was received on 10/30/2014 as Amendment 9. The IR questions, the response of the sponsor and review of the responses are discussed below.

#### Analytical Method Validation Report, 138VAL730 IP 13 FC 139/01

- a. For specificity in Section 6.3, table 4, you

. Please provide data demonstrating the (b) (4) to demonstrate the specificity of your assay.

Response: The sponsor included data which demonstrated that the (b) (4)

Review of Response: This demonstrates the specificity of the assay as the (b) (4)

- b. In Table 5, you presented data showing a summary of the approval of linearity and parallelism for (b) (4) two Drug Products analyzed vs the 8<sup>th</sup> IS and (b) (4) by the One-Stage Clotting Assay but did not provide the actual data. Please provide the actual data demonstrating parallelism of the drug product and the standard (b) (4), including representative plots over the range of the assay (at the minimum (b) (4) of the target concentration in the drug product).

Response: The sponsor provided figures illustrating linearity and parallelism between house standard (b) (4) and the drug product in the range of (b) (4) as the starting concentration of sample, as well as an illustration of the statistical analysis carried out to determine linearity and parallelism using a validated program (b) (4)

Review of Response: The presented data is adequate for illustration of linearity and parallelism of the assay.

- c. Please provide data included to explain why (b) (4) of the data in Table 5 failed to meet the acceptance criteria. For the drug product lot (b) (4), the linearity was “rejected” but parallelism was not rejected. It is not clear to us how that is possible. Please explain.

Response: Data were provided in the form of a graphical representation of the results as well as clarification of the parameters used for statistical analysis, to illustrate the two discrepant findings in the linearity and parallelism study.

Review of Response: The presented data clarifies how it is possible to reject data due to lack of linearity even though the curves are parallel, and vice versa.

- d. In section 6.5, the accuracy of the method is demonstrated by comparing the potency of (b) (4) Drug Product measured using the house standard (b) (4) to that measured using the 8<sup>th</sup> International Standard. We do not agree that these results demonstrate accuracy of your method. It only demonstrates that the two standards give comparable results (standard qualification). Please provide data demonstrating accuracy of your method by spiking your drug product with known quantities of your in-house standard or the IS over the range of your assay (at the minimum (b) (4) of the target concentration in the drug product).

Response: Octapharma provided details of an experiment where three concentrations of (b) (4) house standard were spiked (b) (4) Drug Product, to cover the range of the assay (b) (4) expected potency). The recovery of samples was between (b) (4) and was within the acceptance criteria for the assay (b) (4)

Review of Response: The included data adequately demonstrates the accuracy of the method.

- e. In section 6.6, intermediate precision, please provide data demonstrating intermediate precision among multiple analysts for the drug product.

Response: The tables demonstrating intermediate precision were updated to include information on the analyst carrying out the assay.

Review of Response: This response is adequate.

The above described information was added to the validation report and the new report, 138VAL730 IP 13 FC 137 FC 139/02 was provided as part of Amendment 9.


## Conclusions



The method and updated validation report are clearly described and contain sufficient information to allow approval of this test method as part of this application.


## 2. Identification by (b) (4)

(b) (4)

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### Method

(b) (4)


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### Method Validation


Validation of the method for determining identity by (b) (4) was documented in Section 3.2.P.5.3 in Validation Report 138VAL723 FC 137 FC 139/02: (b) (4) drug product of Human-cl rhFVIII.”

Validation was performed in conformance with ICH Q2 (R1) guidelines, which requires the assessment of the Specificity for validation of an identity test.


(b) (4)

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(b) (4)

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(b) (4)




(b) (4)



(b) (4)




(b) (4)




Conclusion

The method is suitable and has been validated adequately as an identity test.

3. (b) (4)




(b) (4)



(b) (4)

(b) (4)





(b) (4)

(b) (4)

(b) (4)

#### First Information Request

Based on the review of the initial submission, IRs were sent to the sponsor on 22 August 2014. The responses were received in Amendment 7 dated October 10, 2014.

- a. Please include in your SOP (130SOP735/04) the (b) (4) the control as a system suitability criterion based on your historical data and submit the revised SOP for review.

Response and Review: Section 5.5 of SOP 130SOP735/05 has been updated to include the (b) (4). The acceptable range has been set to (b) (4) based on historical data (b) (4). The response is satisfactory.

- b. Section 5.5 of the SOP (130SOP735/04) states that “The (b) (4) (b) (4)” Please clarify (b) (4) and provide the justification for the acceptable N value with your historical data.

Response and Review: The (b) (4) is determined (b) (4) justified by historical data (b) (4) the mean and standard deviation were (b) (4) respectively. Section 5.5 of SOP 130SOP735/05 is updated to specify (b) (4) (b) (4). A review of the section 6.1.4 of the revised validation report, 138VAL735/05, shows that the (b) (4) was well above the new limit. The response is satisfactory.

- c. It is not clear how you perform (b) (4). Please clarify whether it is done (b) (4). We recommend that you (b) (4) because the results cannot be considered objective when (b) (4).

Response and Review: The (b) (4) is using (b) (4).  
The response is acceptable.

- d. Since this method is also used as an identification test for the Human-cl rhFVIII protein, please revise the SOP to include a description of how the rhFVIII is identified by this method and submit for our review.

Response and Review: The identification of the rAHF sample is performed by (b) (4). Section 6.2 of the revised SOP 130SOP735/05 indicates that (b) (4).  
The response is acceptable.

- e. The (b) (4) provided in the SOP (130SOP735/04) and validation report (138VAL735 IP 137, FC 139/03) show that (b) (4). The estimation of (b) (4) may be significantly affected by (b) (4) method, if performed (b) (4). Please explain how you ensure that the results are obtained objectively and consistently from lot to lot.

Response and Review: Section 6.1 of the revised SOP 130SOP735/05 indicates that (b) (4) is performed. If the (b) (4) is not successful, the (b) (4). The sponsor included a figure in this section to provide instructions on (b) (4) particularly where (b) (4). The (b) (4) procedures are clearly described in the revised SOP, 130SOP735/05. The response is acceptable.

- f. The experimental design of your accuracy study involves measurement by two (b) (4) methods (b) (4). Your results show comparability (b) (4) because the latter results are below LOQ. Please provide data for (b) (4), which are above LOQ from both methods to demonstrate that the results obtained by the methods are comparable.

Response: An additional experiment was designed to evaluate comparability of the (b) (4) between two methods. (b) (4).  
The results provided in Table 5 of the updated validation report, 130SOP735/05, from samples containing (b) (4). No statistically significant difference between the methods within a confidence interval of 99% ((b) (4)) was observed. The data demonstrated that (b) (4) are comparable between (b) (4) methods when samples contain (b) (4).

The comparability of (b) (4) between two methods is demonstrated by using samples (b) (4). The results provided in Table 6 of the updated validation report, 130SOP735/05, from samples (b) (4), were evaluated using (b) (4). No statistically significant difference between the methods within a confidence interval of 99% (b) (4) was observed. The data demonstrated that (b) (4) are comparable between (b) (4) methods when samples contain (b) (4).

The submitted data showed comparable results between (b) (4) methods when the (b) (4) are above the LOQ (b) (4). The response is satisfactory.

### Second Information Request

Based on the review of the initial submission, and subsequent IRs, a second IR was sent to the sponsor on 20 January 2015.

1. We disagree with your LOQ conclusions for (b) (4). The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. You have provided precision results at (b) (4) (proposed LOQ) but not the accuracy data at this level. For (b) (4) this is an impurity test. Therefore, LOQ is a critical validation characteristic. Please provide the accuracy data to demonstrate the accuracy at (b) (4).
2. Please provide the reference 18 cited in validation report page 34 "Study Report OC11-0289 (b) (4) method development for (b) (4)".  
You referred to this document for the results of the (b) (4) method you used (b) (4) but did not submit the document.

### Conclusion

The (b) (4) method for (b) (4) is clearly described in the SOP. However, there are outstanding issues with the method validation as discussed in the second IR.


### **4. Total Protein Content by (b) (4)**

The assay is used to determine the protein concentration of drug product, (b) (4). The lot-release specification for the final container, Nuwiq®, formulations are: (b) (4) (250 IU), (b) (4) (500 IU), (b) (4) (1000 IU) and (b) (4) (2000 IU).


### Method

(b) (4)

(b) (4)




(b) (4)




Validation

This method was validated as a quantitative assay for drug product (138VAL740IPFC137FC139/01). The characteristics validated include: specificity, linearity, range, accuracy, repeatability, intermediate precision, and robustness.


(b) (4)




(b) (4)




(b) (4)




(b) (4)



(b) (4)



(b) (4)



#### Conclusion


The selection of validation characteristics and acceptance criteria for this assay are appropriate, and the acceptance criteria were met in the validation. The assay is validated for its intended applications.

#### **5. Moisture Content by (b) (4) )**

The residual moisture of the final drug product was measured by (b) (4) . The proposed specification for water content of drug product is (b) (4) (w/w) for all dosage formulations.

#### Method

(b) (4)





(b) (4)

(b) (4)

#### Validation

The method was validated as a quantitative assay for drug product (138VAL714FC 139/01), the assay characteristics validated include: specificity, linearity, range, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), and robustness.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

#### Information Request and Review

IR questions concerning this method were sent on August 22nd, 2014, and the sponsor submitted the responses in Amendment 7 on October 10, 2014:

IR Question: You have demonstrated linearity, range, LOD and LOQ using water standard only. Please provide results of evaluation of these characteristics within the drug product matrix.

Response: In the updated validation report 138VAL714 FC139/02, section 6.5.5.3 demonstrates the linearity of response of residual water in the drug product matrix. The range for the product was verified by the linearity (section 6.5.5.3), accuracy (section 6.5.5.2) and the repeatability (section 6.6.5) within the range of (b) (4) w/w meaning the effective LOQ for the method is (b) (4). LOD could only be evaluated using standard samples as it is not possible to produce vials with low enough residual moisture to reach the LOD of this method. The corresponding Master SOP 130SOP714 has been updated to include the valid range of residual water in drug product of Antihemophilic Factor (Recombinant).

Review of the response: In the updated validation report, the final container drug product (b) (4)

(b) (4)

. Taken together data from repeatability and accuracy studies, the range of the method was also verified to be between (b) (4), and the LOQ is defined to be (b) (4). Based on the response provided in Amendment 7, it can be concluded that the linearity, range and LOQ of the method has been adequately validated, and the method has been validated for its intended use.

#### Conclusion

The selection of validation characteristics and acceptance criteria for this assay are appropriate, and the acceptance criteria were met in the validation. The assay is adequately validated as a release test for the drug product.

#### **6. Arginine**(b) (4)

L-Arginine is an excipient, (b) (4)

The proposed specification is (b) (4) for all drug product formulations (250, 500, 1000 and 2000 IU/vial of recombinant factor VIII).

#### Method

(b) (4)

(b) (4)

#### Validation

The method was validated as a quantitative assay for the drug product (138VAL160FC139/01). The assay characteristics evaluated include: specificity, linearity, range, accuracy, repeatability, intermediate precision, and robustness.

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

#### Conclusion


The selections of validation characteristics and acceptance criteria for this method are appropriate, and validation characteristics such as specificity, accuracy, repeatability, intermediate precision, and robustness, have been validated. The method is approvable as a lot-release test of the drug product.

#### **7. Sucrose by (b) (4)**

Sucrose is an excipient used in the Human-c1 rhFVIII drug product. The drug product specification for sucrose is (b) (4) for all drug product formulations.

#### Method


The sucrose concentration in the Human-c1 rhFVIII drug product is determined by (b) (4)




#### Method Validation

The method is used as a quantitative assay procedure for sucrose in the Human-c1 rhFVIII drug product. The following validation characteristics were evaluated: specificity, linearity, range, accuracy, repeatability and robustness.


(b) (4)





(b) (4)



(b) (4)



(b) (4)

(b) (4)

First Information Request

The following IR was submitted to the sponsor on 22 Aug 2014. The response by Octapharma received as Amendment 7 on 10 Oct 2014, is discussed below.

- a. We have the following questions/comments regarding the Method validation report, Document 138VAL168FC139/01:

- i. In your specificity studies (section 6.1) (b) (4)

Please explain how an acceptance criterion for (b) (4)  
was set at (b) (4)

What is the upper limit of the acceptance criteria?

Response: (b) (4)

Review: The sponsor has revised the acceptance criteria for (b) (4)

and section 6.1.3.1 (document 138VAL168 FC139/02) was updated accordingly. The sponsor's response is appropriate.

- ii. As per the data presented in Table 1 (section 6.2), you have studied linearity using sucrose standard, analyzed at different concentrations. Please provide data including linear regression plots using your product samples and demonstrate parallelism between standard and final container product regression lines to establish linearity of the assay.

Response: The Table 3 and Figure 4 show that the determination of sucrose in the sample is performed in parallel with the determination of sucrose in the standard solutions. The section 6.4.4 in the validation report 138VAL168 FC 139/02 has been updated.

- iii. You have determined accuracy (section 6.3) at the target concentration only but not over the range of the assay. Please provide data for accuracy determined over the intended range of the assay.

Response: In addition to data presented in response b, recovery data is included in the Table 4 and Table 5, showing that accuracy and precision could be demonstrated in the linear range of the standard range (b) (4). The tables are included in section 6.4.4.1 of the updated validation report 138VAL168 FC 139/02. The test was performed on two different occasions. On the first occasion the sample was (b) (4) whereas on the second occasion the sample was (b) (4).

- iv. You have established range (section 6.2) by analyzing linearity and accuracy of sucrose standards. Range should be determined based on the results obtained from the product samples. Please provide data for linearity, accuracy and repeatability obtained from the product samples to establish range of the assay.

Response: In the updated validation report 138VAL168 FC 139/02 the range (b) (4) concerning accuracy (see response c), linearity (see response b) and precision (see response b) for the sample, shows that the method is suitable for determination of sucrose in the range as stated for the standard solutions (b) (4). The sample is diluted into that range by diluting the sample (b) (4), please refer to section 5.1 in the SOP 130SOP168/04.

Review of responses to ii, iii, & iv: In the updated validation report submitted by the sponsor, the linearity of both samples and standards were analyzed at different concentrations. The response of the sucrose standard was linear in the range of (b) (4), with a correlation coefficient of  $\geq 0.995$  and a random distribution of residuals. Linearity in samples was determined from the accuracy data obtained on two occasions. In one experiment, sucrose was (b) (4). The sucrose concentration of (b) (4) in the native samples was taken as 100% of the nominal value. (b) (4). In the second experiment, (b) (4). Thus, accuracy and linearity were determined in the range of (b) (4) sucrose. A new IR was submitted to the sponsor to submit appropriate accuracy and linearity data in product samples covering at least (b) (4) of the targeted range of (b) (4) (corresponding to (b) (4) of sucrose in the sample), and establish range based on the revised accuracy/linearity results.

- v. You have not studied intermediate precision (section 6.4) and have referred to the validation report of another product stating that 'where RSD was even lower for intermediate precision than for repeatability, it is not considered necessary to investigate intermediate precision in the validation'. However, intermediate precision should be established for the product under consideration. Please submit appropriate intermediate precision data to show that the assay variability is within the acceptable range.

Response: In the Table 6 and in section 6.5.4 in the updated validation report 138VAL168 FC139/02 repeatability and intermediate precision on batch C425A139 have been determined.



Review: The sponsor has submitted the revised validation report where intermediate precision was evaluated from (b) (4). The overall RSD was (b) (4) and within the acceptance criteria of (b) (4). The sponsor's response is satisfactory.

b. Robustness studies (section 6.5)

- i. You have studied robustness by testing sucrose standard solution. Please provide results of robustness of the method using your final container product.

Response: In section 6.6.5.1 of the updated validation report 138VAL168 FC 139/02 it could be concluded that a (b) (4)

Although the retest showed approved (b) (4), the method has been updated with (b) (4).

Review: The sponsor has revised the acceptance criteria for (b) (4) in the (b) (4), and section 6.1.3.1 (document 138VAL168 FC139/02) was updated accordingly. The sponsor's response is appropriate.

- ii. Please specify an acceptance criterion for the 'deviation' in the sucrose quantification results for the evaluation of (b) (4) (section 6.5.1.2).

Response: When repeating the robustness tests by evaluating the (b) (4) was approved. Please see section 6.2.4.2 in the updated validation report 138VAL168 FC 139/02.

(b) (4)

(b) (4)

(b) (4)

Review: The updated validation report submitted by the sponsor includes the acceptance criteria for deviation in the sucrose quantification results, and is acceptable.

- iii. Your robustness data indicates (b) (4). Accordingly, please modify your SOP (Document 130SOP168/03, section 5.3) to reflect the acceptable (b) (4) as determined in the validation studies.

Response: The update SOP 130SOP168/04, section 5.3 includes that (b) (4)

Review: As requested by CBER, the sponsor has submitted the revised SOP which includes (b) (4).

- iv. Resolution between sucrose and (b) (4) is studied as a part of (b) (4) criteria in the validation studies. This parameter is not described in the method

SOP (Document 130SOP168/03) as (b) (4). This is a critical attribute for your test. Please revise the method SOP to include the above (b) (4) criterion.

Response: Since (b) (4)

(b) (4) see section 6.2.2 in the validation report 138VAL168 FC 139/02.

Review: The drug product (b) (4)

(b) (4) was not evaluated as a critical parameter. The response is acceptable.

### Second Information request

After the review of response to the first IR, a new IR was submitted to the sponsor on 16 January 2015.

- A. In your accuracy determinations (Document 138VAL168 FC 139/02, section 6.4.2) it is stated that (b) (4)

(b) (4) In our previous IR (dated 22 August 2014), we requested linearity and accuracy data of your product samples in the intended assay range. For the reasons explained above, the data that you have provided do not adequately address our IR. Please provide appropriate linearity and accuracy data to support your proposed assay range for sucrose.

- B. The results presented in tables on pages 41 and 42 appear to be incorrect. The mean measured sucrose concentration represented as (b) (4) (page 41) and nominal sucrose concentration and corresponding measured value represented as (b) (4) respectively (page 42) of the revised validation report. Please confirm the errors and provide the corrected table.

### Conclusion



The method is clearly described in the SOP. However, there are outstanding issues with the method validation as discussed in the second IR.

### **8. Poloxamer 188 Content by (b) (4)**

The quantities of Poloxamer 188 are measured by (b) (4)


Method

(b) (4)


Method Validation

This is a quantitative method. The following characteristics were studied to validate the method: specificity, range, linearity, LOQ, accuracy, repeatability and intermediate precision).



(b) (4)






(b) (4)



(b) (4)



(b) (4)



Conclusion

Suitability of the Poloxamer 188 procedure as a lot release test of drug product samples has been satisfactorily demonstrated.

**9. Sodium Content by (b) (4)**

The assay uses (b) (4) method. The proposed specification is (b) (4) for all dosage formulations.

Method

(b) (4)

(b) (4)


(b) (4)

Method Validation

The following characteristics were studied to validate the method: linearity, range, specificity, accuracy, precision (repeatability and intermediate precision), LOQ, and robustness. This is a quantitative method.

(b) (4)

(b) (4)



### Conclusion


Suitability of the Sodium procedure has been satisfactorily demonstrated for assay of the drug product samples.

### **10. Chloride by (b) (4)**

The test was done as described in (b) (4). The proposed specification is (b) (4) for all dosage formulations.

### Method

(b) (4)



### Method Validation

This quantitative method is validated by evaluating the characteristics of specificity, accuracy, precision, linearity, range, LOD/LOQ and robustness.

(b) (4)

(b) (4)

### Information Request

A following IR was sent to the sponsor on August 22, 2014. The response was received on September 4, 2014 in the amendment 4.

Your proposed specification for chloride, (b) (4) is inconsistent with the calculation presented in your SOP (130SOP131/05) in which chloride is expressed in (b) (4). Please revise either the SOP or the specification to be consistent.

Response: In the revised SOP 130SOP131/07 the calculation from (b) (4) has been included.

Review: The new version SOP (130SOP131/07) is submitted. The conversion from (b) (4) is clearly described in the section 5.3 of the SOP. The response is satisfactory.

Conclusion


This method of chloride determination is validated adequately for the intended use.

**11. Citrate by (b) (4)**

This assay is performed in accordance with a (b) (4) method. The proposed specification for the drug product is (b) (4) for all dosage formulations.

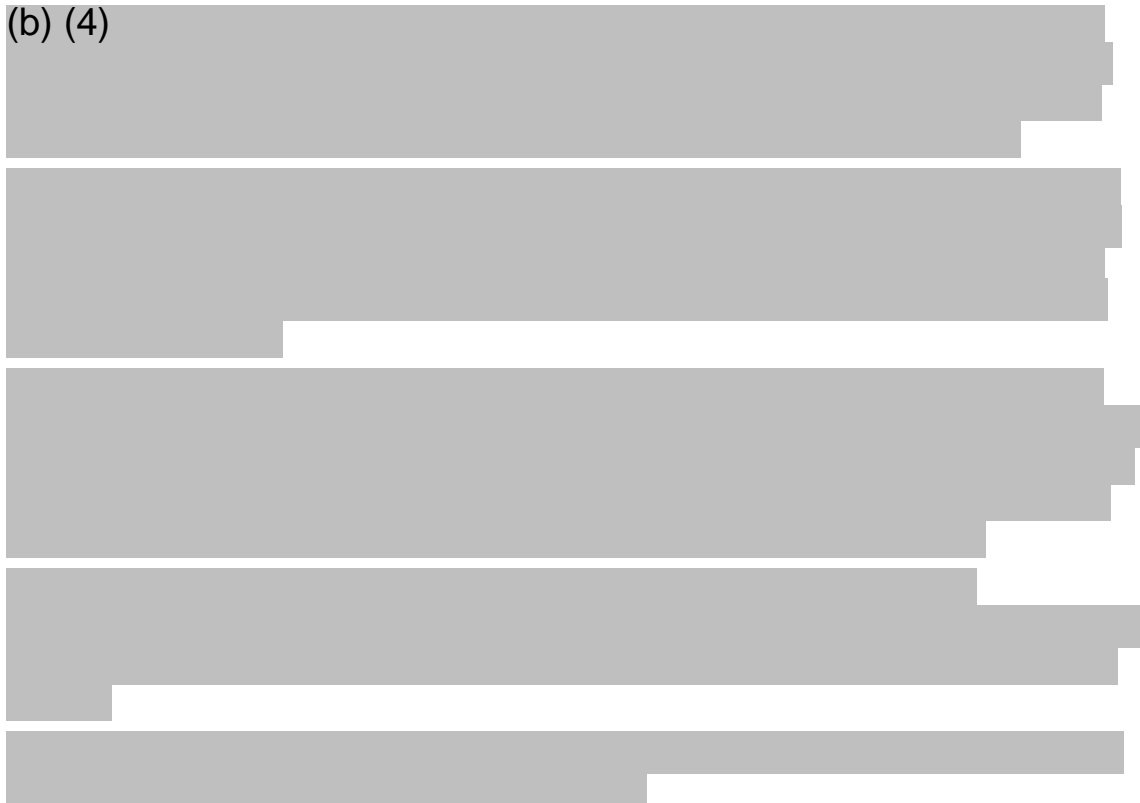
Method

(b) (4)

Method Validation

This quantitative method is validated by evaluating specificity, accuracy, precision, linearity, range, LOQ and robustness.

(b) (4)



(b) (4)

### Information Request

Five IRs were sent to the sponsor on 22 August 2014. The responses were received on 4 September, 2014 in the amendment 4.

- a. Your proposed specification for citrate, (b) (4), is inconsistent with SOP (130SOP032/03) presented in your SOP in which citrate is expressed in (b) (4). Please revise either the SOP or the specification to be consistent.

Response: In the revised SOP 130SOP032/4 the calculation from (b) (4) has been included.

- b. In your SOP (130SOP032/03) you mentioned that (b) (4) may be used for the assay. However, you have used (b) (4) column during validation. You have not shown equivalency of results between (b) (4) during method validation/robustness. Please provide appropriate data to demonstrate equivalency (b) (4).

Response: In the revised SOP 130SOP032/04 a clarification has been done that only (b) (4) is used for Antihemophilic Factor (Recombinant) (rAHF) (Human-cl rhFVIII).

- c. Your SOP (number 130SOP032/03) does not describe procedure(s) for sample preparation for the drug product. Please revise the SOP to add the sample preparation procedure(s) and resubmit for review.

Response: In the revised SOP 130SOP032/04 the sample preparation has been included.

- d. Your SOP (number 130SOP032/03) instructs to use (b) (4). However, you have conducted your validation using (b) (4). Please provide data to show that (b) (4) are equivalent for your assay.

Response: In the revised SOP 130SOP032/04 a clarification has been done that only (b) (4) is used for rAHF (Human-cl rhFVIII).

- e. Please specify the storage temperature of the prepared samples for the robustness study (page 20 of 22) in the validation report.

Response: The revised validation report 138VAL032 FC 139/02 has been updated with the storage temperature for the samples during the robustness study.

Review of the responses: The new version SOP (130SOP032/04) is submitted. The conversion from (b) (4) is clearly described in section 6.3.1 of the SOP. In section 3.1, it is stated that for Human-cl rhFVIII DP only (b) (4)



(b) (4) is used. A new section 5.1.1.4 describes sample preparation of Human-cl rhFVIII DP and only (b) (4)

A revised version of the validation report (138VAL032 FC 139/02) is submitted. The storage temperature is indicated as (b) (4) in the section 5.7.2. The responses are satisfactory.

### Conclusion

This method of citrate determination is adequately validated for the intended use.

### **12. Calcium by (b) (4)**

This assay is performed using (b) (4). The proposed specification for the drug product is (b) (4) for all dosage formulations.

### Method

(b) (4)

### Method Validation

The method is used as a quantitative assay procedure in the Human-c1 rhFVIII drug product. The following validation characteristics were evaluated: specificity, linearity, range, accuracy, repeatability, intermediate precision and robustness, using Calcium (b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

First Information request

The following IR was submitted to the sponsor on 22 August 2014. The response by Octapharma received as Amendment 4 on 02 Sept 2014, is discussed below.

- a. Please address the following questions regarding your analytical procedure, Document 130SOP708/04:
  - i. You have experimentally evaluated the (b) (4) of the samples. Please provide the procedure and results obtained with your samples. How different is this value from the one obtained with the standard calcium solution?

Response: It should be pointed out that the factor (b) (4) in the formula under paragraph 5 Evaluation in 130SOP708 could be mistaken as the (b) (4), but (b) (4). However the (b) (4)

level. For clarification the description and formula in the SOP 130SOP708/05 under paragraph 5 has been revised.

Review: The sponsor has revised the formula and text in the method SOP (section 5.0). The calcium in the drug product is determined from the formula using (b) (4) of the standard/sample and known concentration of the standard. The sponsor's response is satisfactory.

- ii. According to your Robustness data, analysis of all samples should be completed (b) (4). Please revise your SOP (section 4.4) to specify the incubation time based on these results.

Response: In the revised SOP 130SOP708/05 the incubation time has been revised for the final container sample.

Review: As requested by CBER, the method SOP (section 4.4) was revised to specify the sample incubation time of (b) (4) for the drug product samples.

- b. We have the following questions/comments regarding the Method validation report, Document 138VAL708FC139/01:

- i. Your method (section 5.4) and Specificity (section 6.1): In your assay procedure calcium concentration is (b) (4)

(b) (4) Please provide an explanation for not using the appropriate negative control. Please also provide data obtained using your matrix blank (containing all components of formulation buffer except calcium) to show that it does not interfere with the assay results.

Response: According to the recovery function shown under paragraph 6.4.4.1.2 in the validation report the (b) (4). This shows that the sample matrix does not disturb the assay and a negative control is not necessary. In addition the found recovery was between (b) (4)

Based on those results and that (b) (4)

Review: The recovery of calcium standards in the drug product varied from (b) (4). The calcium response was linear in the range of (b) (4)

99%

confidence level. The slope ratios of standard and sample were in the acceptable range. These results conclude that the matrix does not interfere with the assay. However, the sponsor's justification for not using water/sample matrix in the blank/negative control is not acceptable. A new IR is being submitted to the sponsor to add appropriate blank/s, and accordingly modify the test method SOP.

- iv. You have indicated range of the assay as (b) (4) by analyzing the linearity/accuracy data of calcium standards. However, based on the linearity/accuracy determinations of your drug product samples, the method is validated in the range of (b) (4) calcium. Therefore, your true assay range is (b) (4) calcium. Please revise the validation report (page 7, section 1.1) and method SOP (page 6, section 5.1) to specify the range as determined using your drug product samples.

Response: The section 1.1 in the validation report 138VAL708 FC 139/02 has been updated with the correct specified range of (b) (4) calcium. Also the revised SOP 130SOP708/05 has been updated with the correct specified range for the final container sample.

Review: The sponsor's response corrects the specified range for calcium in the revised validation report and method SOP, and is acceptable.

Second Information request

After the review of response to the first IR, a new IR was submitted to the sponsor on 16 January 2015.

You have stated in your response to CBER IR (Received on 02 September 2014) regarding section 5.4 of document 138 VAL708FC139/01 that due to negligible interference from the product matrix, and that (b) (4)

(b) (4) . We do not agree with your justification. Since you are using (b) (4)

(b) (4) the sample. Please provide additional explanation or include appropriate blank preparation in the test method and revise your SOP document.

Conclusion

The method is clearly described in the SOP. However, there are outstanding issues with the method validation as discussed in the second IR.

**13. Appearance (Lyo Cake) by Visual Inspection, Solubility of freeze-dried final products, and Visual inspection of solutions**

Method

Appearance of freeze-dried (lyo cake) final container product is evaluated by performing a visual inspection concerning the appearance of the product with regard to the requirements stated in the specifications. Solubility of freeze-dried final products is evaluated by the measurement of the time to complete dissolution of the final container products in the prescribed solvent. Visual inspection of solutions is performed to check the appearance of the reconstituted product with regard to the requirements stated in the specifications. In this application, all three methods were combined and described in one single SOP, 130SOP006/04, and the procedures are in accordance with (b) (4).

Validation

The method (including Appearance of freeze-dried final products, Solubility of freeze-dried final products, and visual inspection of solutions) was not validated. But the testing involves simple visual inspection. Thus, not validating the method is acceptable.

Conclusion

The assay is approvable as a lot release test of the drug product.

**14.** (b) (4)

Method

(b) (4)

(b) (4)

Validation

The method is partially validated by evaluating precision, and robustness.

(b) (4)

Conclusion

This method of (b) (4) is a compendial method. The partial validation of the method is adequate for the intended use.

15. (b) (4)


Method

(b) (4)

(b) (4)

(b) (4)

(b) (4)



Conclusion

This method of (b) (4) is a compendial method. The validation of the method is adequate for the intended use.