



From Grainne Tobin, DBSQC/OCBQ
Noel Baichoo, DBSQC/OCBQ
Tao Pan, DBSQC/OCBQ
Parmesh Dutt, DBSQC/OCBQ
Kouassi Ayikoe, DBSQC/OCBQ
Ritu Agarwal, DBSQC/OCBQ
Mark Levi, DBSQC/OCBQ
Hsiaoling Wang, DBSQC/OCBQ
Alfred Del Grosso, DBSQC/OCBQ
Lokesh Bhattacharyya, DBSQC/OCBQ

To STN: #125577/0

Through William M. McCormick, Director, DBSQC/OCBQ

Sponsor Baxter Healthcare Corporation

Subject: Primary Discipline Review Memo Biological License Application for Quality Control Lot-release Test Methods for the Drug Product for von Willebrand Factor (Recombinant)

Summary of Review

The new Biological License Application (BLA) was submitted for recombinant von Willebrand Factor by Baxter Healthcare Corporation (STN: 125577). This is the Primary Discipline Review memo for the quality control lot-release test methods for the drug Product, including the following analytical methods and their validations, as used for the lot release of the drug product.

1. Determination of Ristocetin Cofactor Activity
2. Determination of the residual FVIII Activity in rVWF Samples
3. Determination of (b) (4)
4. Determination of (b) (4)

5. Purity and identity of rVWF by (b) (4)
6. Determination of VWF (b) (4)
7. (b) (4)
8. Residual Moisture Content by (b) (4)
9. Mannitol and Trehalose dihydrate contents
10. Determination of Polysorbate 80 by (b) (4)
11. Determination of the Glycine Content in Recombinant rVWF by (b) (4)
12. Determination of Citrate Content in Recombinant rVWF by (b) (4)
13. Sodium Content by (b) (4)
14. (b) (4)
15. (b) (4)
16. Appearance of Lyophilized Cake
17. Appearance of Reconstituted solution and Reconstitution time
18. Determination Particulate Matters by (b) (4)

Based on the review of the original BLA submission and the subsequent response from the sponsor, it is concluded that all methods listed above have been described and validated adequately, except “Determination of Polysorbate 80 by (b) (4)” assay, the validation of which has a few deficiencies. An IR was submitted. The response to this IR will be reviewed as an Addendum Memo.

Background

Baxter Healthcare Corp. submitted a new BLA for a drug product (BAX-111), which is a recombinant von Willebrand factor (rVWF). It is indicated in adults diagnosed with von Willebrand disease for the prevention and treatment of bleeding episodes. The rVWF protein is genetically expressed in Chinese Hamster Ovary cells. (b) (4)

The rVWF protein is (b) (4)

. The recombinant VWF is formulated for intravenous injection. It is proposed to be available as single use vials containing nominal potencies of 650 and 1300 IU/vial, and is reconstituted in water for injection before administration (reconstitution volumes: 5 mL for 650 IU/vial, and 10 mL for 1300 IU/vial formulations).

Submitted Information Reviewed

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

- 125577/0.0 – 3.2.P.5.1 Control of Drug Product – Specification(s) Recombinant von Willebrand Factor Final Drug Product (650 IU/vial and 1300 IU/vial)
- 125577/0 3.2.P.5.2 Analytical Procedures
 - Control Test Procedure: VN1306081TB-CTP00.05: Determination of Ristocetin Cofactor Activity according to (b) (4)

- Control Test Procedure, VN1306101TB-CTP00.03: Determination of the residual Factor VIII Activity in rVWF samples
 - Control Test Procedure, VN-13-06136TB-CTP00.02: Determination of VWF (b) (4)
 - Control Test Procedure, VN1306113TB-CVR00.03: Determination of (b) (4) in recombinant VWF samples
 - Control Test Procedure, OR-13-00127-CTPX1.04: Test Method for (b) (4)
 - Control Test Procedure, OR1300693-CTPX1.03: Detection of purity and identity of rVWF with (b) (4)
 - Control Test Procedure, OR1100019-CTPX1.04: Determination of the (b) (4)
 - Control Test Procedure, VN11 04033TB-CTPX3.01: Determination of the Residual Moisture Content
 - Control Test Procedure, NE-40-1100131-CTP/Ver.5: Determination of the Mannitol and Trehalose dihydrate content
 - Control Test Procedure, VN-11-04053TB-CTP00.02: Determination of Polysorbate 80 by (b) (4)
 - Control Test Procedure, VN-11-04082TB-CTP00.01 Determination of Sodium Content (b) (4)
 - Control Test Procedure, OR1400027-CTPTV.01: Determination of (b) (4)
 - Control Test Procedure, VN1104058TB: Determination of (b) (4)
 - Control Test Procedure, OR1400028-CTPTV.01: Determination of Appearance, Appearance of reconstituted solution and Reconstitution time
 - Analytical Procedures [Particulate Matters]
- 125577/0 3.2.P.5.3 Validation of Analytical Procedures
- Consolidated Validation Report, VN-13-06081TB-CVRX1.06: Determination of Ristocetin Cofactor Activity according to (b) (4)
 - Consolidated Validation Report, VN1306101TB-CVR00.03: Determination of the (b) (4) in rVWF samples
 - Consolidated Validation Report, VN-13-06136TB-CVR00.02: Determination of vWF (b) (4)
 - Consolidated Validation Report, OR1300127-CVRX1.04: (b) (4)
 - Consolidated Validation Report, OR1300693-CVRX1.02: Detection of purity and identity of rVWF with (b) (4)
 - Consolidated Validation Report, VN 1306113TB-CVROO.03, Determination of (b) (4) (b) (4)
 - Consolidated Validation Report, VN-11-04033TB-45-VB.01: Determination Residual Moisture
 - Consolidated Validation Report, OR1100019-CVRX1.04: Determination of the (b) (4)
 - Consolidated Validation Report, 2014-AA-rVWF Mannitol_Trehalose_CVR/Ver.01: Determination of D-Mannitol and α - α -Trehalose in rVWF FC

- Consolidated Validation Report, VN1104053TB-CVRX3.02: Determination of Polysorbate 80
- Consolidated Validation Report, VN1104082TB-CVRX4.02: Determination of Sodium Content (b) (4)
- Consolidated Validation Report, VN1104058TB: Determination of (b) (4)
- Consolidated Validation Report, 406. 714-CVRX1.01: Counting of invisible particles (b) (4) in the product rVWF
- 125577/0.0 - 3.3.S.5 Reference Standard or Materials
- 125577/0.0 - 3.2.P.5.6 Justification of Specification(s)
- 125577/0.5 1.12.4 Request for Comments and Advice-Response to RFI, Response to 23 April 2915 FDA Information Request, response received 8 May 2015
 - Control Test Procedure, NE-40-1100131-CTP/Ver.7: Determination of the Mannitol and Trehalose dihydrate content
- 125577/0.5 3.2.P.5.3 Validation of Analytical Procedures
 - Consolidated Validation Report, VN1306101TB-CVR00.04: Determination of the (b) (4) in rVWF samples
 - Consolidated Validation Report, OR1300127-CVRX1.05: (b) (4)(b) (4)
- 125577/0.6 1.2 Response to FDA information request dated 23 April 2015, Received on 22 May 2015
- 125577/0.6 3.2.P.5.3 Analytical Procedures
 - Control Test Procedure, VN1306113TB-CVR00.04: Determination of (b) (4) in recombinant VWF samples
 - Control Test Procedure, VN-11-04053TB-CTP00.03: Determination of Polysorbate 80 by (b) (4)
 - Control Test Procedure, VN-11-04053TB-CTP00.03: Determination of Polysorbate 80 by (b) (4)
 - Control Test Procedure, VN-11-04082TB-CTPX1.03 Determination of Sodium Content (b) (4)
- 125577/0.6 3.2.P.5.3 Validation of Analytical Procedures
 - Consolidated Validation Report, VN-13-06136TB-CVR00.03: Determination of VWF (b) (4)
 - Consolidated Validation Report, VN 1306113TB-CVROO.04: Determination of VWF (b) (4)
 - Consolidated Validation Report, VN1104082TB-CVRX4.03: Determination of Sodium Content (b) (4)
 - Study Report OR-13-00127-05-SB.02: (b) (4)
 - Consolidated Validation Report, VN1104053TB-CVRX3.03: Determination of Polysorbate 80

Review Narrative

1. Determination of Ristocetin Cofactor Activity

The analytical procedure described for measurement of potency is an assay of the VWF:RCo activity and is used to measure the potency of the BAX-111 rVWF drug product (DP) (b) (4) [redacted]. The proposed nominal dosages for the drug product are 650, and 1300 IU/vial. The specifications are (b) (4) [redacted], which is the target fill 130 IU/mL (b) (4) [redacted]. The sponsor provided the Control Test Procedure VN1306081TB-CTP00.05 and the Consolidated Validation Report VN-13-06081TB-CVRX1.06.

Method

(b) (4)

(b) (4)

The following IR was submitted to the sponsor on April 23, 2015. The response was received on May 7, 2015 as Amendment 0.5. The IR questions, the response of the sponsor and review of the responses are discussed below.

- a. We have the following information request regarding your CTP, document number VN1306081TB-CTP00.05
 - i. In section 5 of your CTP, it is not clear how you fit your sample and reference curves. Please clarify if you are using linear or non-linear curve fit. If curve fitting is not linear regression, please explain the meaning of “slope” and “slope ratio” because slope of each curve changes at every point for a non-linear curve.

Review of Response: The sponsor uses the linear curve fit and parallel line analysis method to determine the potency as per (b) (4) [redacted] to calculate potency. The answer has been answered appropriately.

- ii. Please provide details of calculation of parallelism for your curve fitting.

Review of Response: (b) (4) [redacted]

- iii. (b) (4) [redacted]

Review of Response: (b) (4) [redacted]

- iv. Please revise section 5 to include acceptable range of slope ratio (based on validation and historical data) as an acceptance criterion and submit for review.

Review of Response: This IR has been addressed satisfactorily in response to IR # 2e below.

- b. We have the following information request regarding your Method validation report, document number VN-13-06081TB-CVRX1.06
 - i. To demonstrate specificity of your method, please provide data to show that the matrix of the drug product (which does not contain VWF:RCo) does not affect the assay results significantly.

Review of Response: The sponsor provided the specificity data which shows that spiking the (b) (4) DP with a known amount of WHO Standard could be quantitated accurately (recovery (b) (4)), demonstrating method specificity.

- ii. Table 3 of your validation report that the results obtained with the standard curves are not valid (n.v.) for the standard (WHO (b) (4)). We do not agree that data from TE1 and TE4 can be included in the evaluation of the validation characteristics. Please recalculate all validation characteristics after excluding the data from TE1 and TE4 and resubmit for review.

Review of Response: The sponsor provided the information that they conducted (b) (4) experiments and included data only from the valid experiments for remainder of the validation studies. The IR has been addressed adequately.

- iii. (b) (4)

Review of Response: (b) (4)

- iv. Please provide appropriate data analysis to show parallelism between the standard and samples for each experiment to demonstrate linearity of your method.

Review of Response: Answer to this IR has been provided above appropriately, it does not need to be discussed here.

- v. In section 5.8.2, your criterion for acceptance of parallelism is (b) (4). This range is too wide. Please justify why this wide range is acceptable, with appropriate calculations and literature reference.

Review of Response: In the response the sponsor stated that the historical data was used to derive these numbers. (b) (4)

The IR has been explained adequately.

vi. (b) (4)

Review of Response: The sponsor explained that there was a typographic error which was corrected in the updated version of the report.

vii. For robustness studies in section 5.10.1.3, the report stated that “Statistical significance is obtained for the analyzers (b) (4) but not for the reagents (b) (4) or operators (b) (4).” Please clarify this statement indicating what your null hypothesis is, what your conclusions are and how you arrived at the conclusions (your calculations).

Review of Response: (b) (4)

Conclusion: The method was adequately described and validated, and can be approved for quality control lot release testing.

2. Determination of the (b) (4)

(b) (4)

Method

(b) (4)

Information Request and Review:

IR questions concerning this method were sent on 23 April 2015, and the sponsor submitted the responses in Amendment 0.5 on 8 May 2015.

i. (b) (4)

[Redacted]

(b) (4)

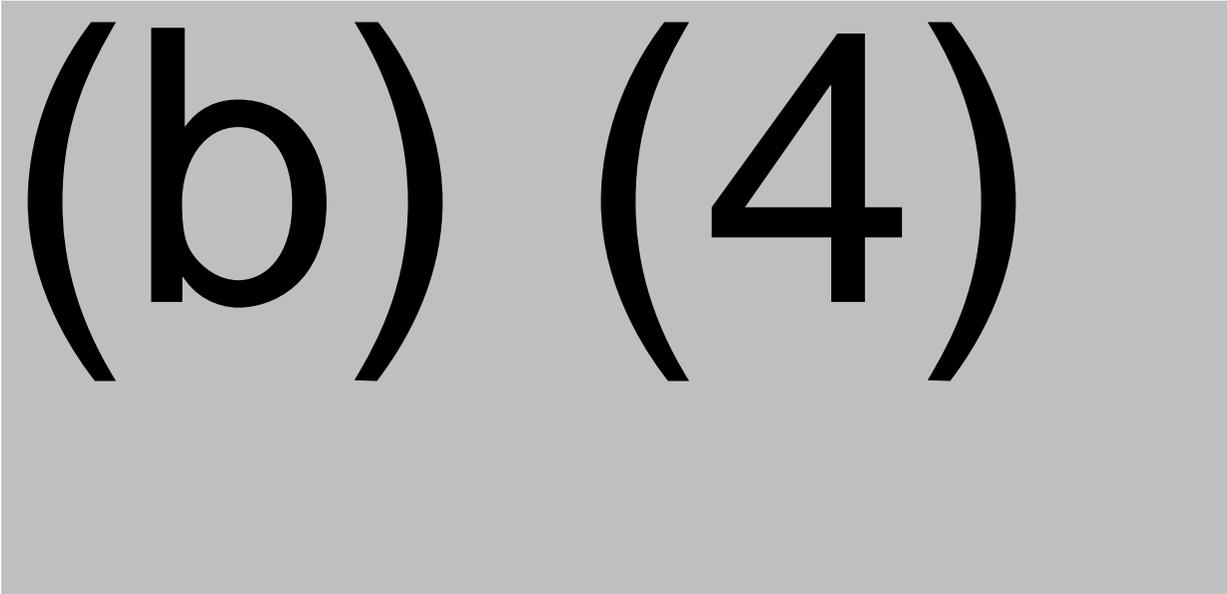
8. Residual moisture determination by (b) (4)

The specification for residual moisture for the final drug product is (b) (4), and it is determined by a (b) (4) method.

Method

(b) (4)

[Redacted]



Conclusion: For the (b) (4) method to determine the residual moisture in BAX-111 drug product, the description is adequate, the selection of validation characteristics and acceptance criteria was appropriate, and the acceptance criteria were met during the validation of the method. The method has been validated for its intended use of drug product release.

9. Mannitol and Trehalose dihydrate contents

Mannitol is used as a (b) (4) and trehalose dihydrate as a (b) (4) in the rVWF drug product. The proposed specifications for mannitol and trehalose dihydrate are (b) (4) and (b) (4) respectively, for both 650 IU/vial and 1300 IU/vail products.

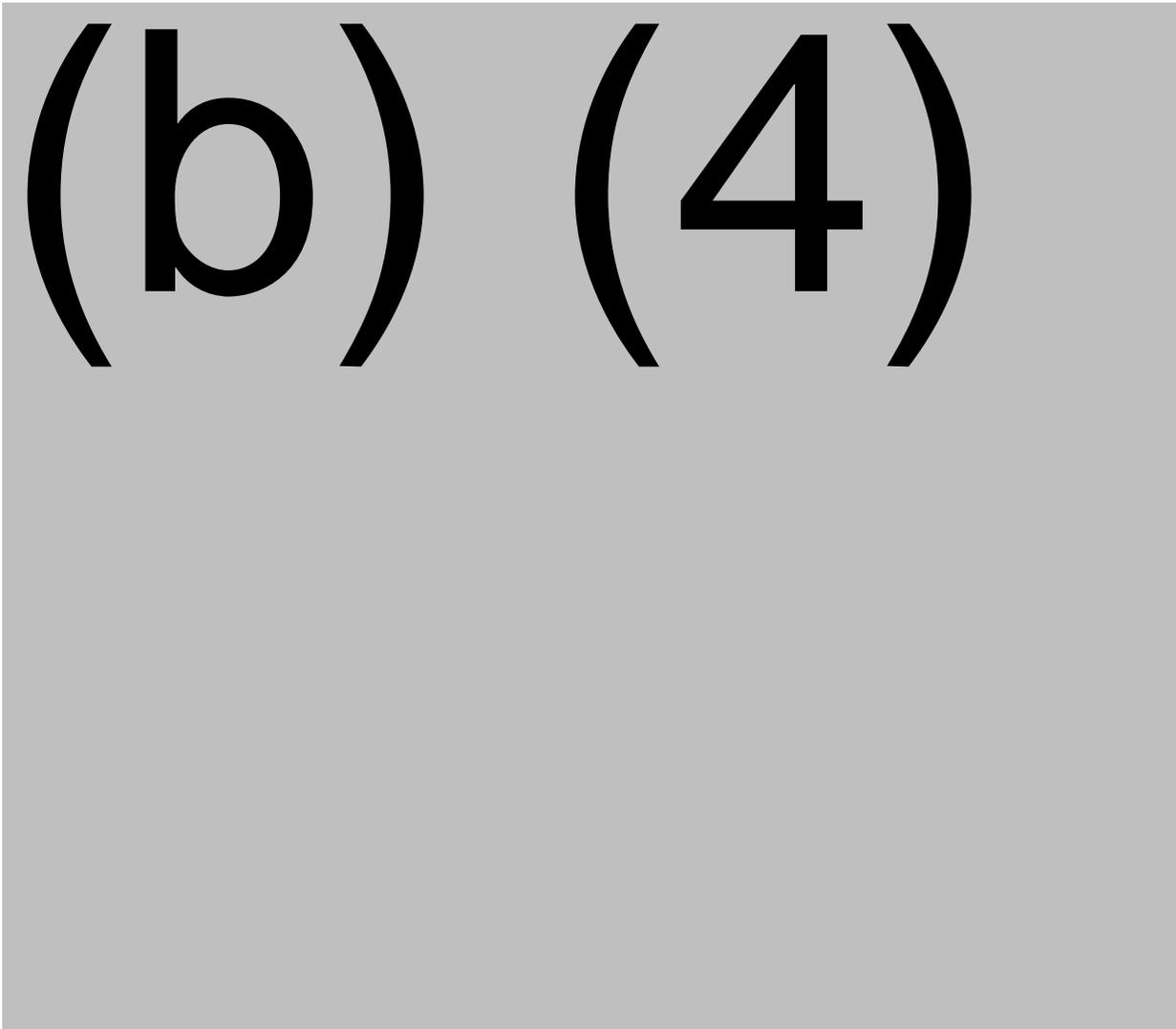
Method

(b) (4)

The text "(b) (4)" is followed by a large, irregularly shaped grey redaction box that covers the majority of the content in this section.

Method Validation

This quantitative method is validated by evaluating specificity, accuracy, precision, linearity, range, and robustness according to the ICH Q2 (R1) guideline.



Information Request and Review

Following IR was sent to sponsor on 23 April 2015. The response was received on 7 May 2015 in amendment 05.

- i. In section 5.1.1 of your SOP the acceptance criterion for (b) (4) [REDACTED] It is not clear what you mean by percent (%). Please clarify this acceptance criterion with supporting data, including calculation or make adequate correction, if necessary.

Review of the response: The sponsor informed that it is a typographic error. The correct acceptance criterion for (b) (4) [REDACTED]. The sponsor also informed that the results of a retrospective review of the accumulated data to support the proposed acceptance criteria for (b) (4) [REDACTED] indicate that the (b) (4) [REDACTED] acceptance criterion should be tightened to (b) (4) [REDACTED]. The acceptance criterion for (b) (4) [REDACTED] was updated in the NE-40-1100131-CTP, ver. 7 document. The response is satisfactory.

Conclusion: The method is described and validated adequately for the intended use.

10. Determination of Polysorbate 80 by (b) (4)

Polysorbate 80 (b) (4) is a process-related impurity in the rVWF drug product and is used to (b) (4). The specification is (b) (4) for drug product strengths 650 IU/vial and 1300 IU/vial.

Method

(b) (4)

Method Validation

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The robustness study data obtained during method development was not included in the submission.

Information Request and Review

First Information request: The following IR was submitted to the sponsor on 23 April 2015. The response by Baxter Healthcare Corporation received as Amendment 6 on 22 May 2015, is discussed below.

We have the following information request for your Method validation report, document number VN1104053TB-CVRX3.02:

- i. In your accuracy determinations (section 4.2), you have not specified the initial polysorbate 80 content in the rVWF drug product. Assuming the polysorbate 80 concentration to be approx. (b) (4) (from the batch analysis results), your validated range is (b) (4). Thus, your accuracy data does not cover the lower specification limit of the product (b) (4). Please provide additional results of accuracy of the method using your drug product, evaluated at minimum (b) (4) of the target concentration.

Review of response: In response, the sponsor submitted the accuracy results obtained by testing (b) (4) sample, which as per the manufacturing process description, does not represent the final container sample. Thus, the sponsor's response is not acceptable. Additional IR is being submitted to the sponsor to demonstrate accuracy/linearity using the drug product.

- ii. Please provide the linearity plot of signal (b) (4) against the analyte concentration (polysorbate 80) for your standard (section 4.6.1).

Review of response: As requested by CBER, the sponsor provided the linearity plot of polysorbate 80 standards in the updated validation report (VN1104053TB-CVRX3.03 section 4.6). Linearity was studied using polysorbate 80 standards in the concentration range of (b) (4). The results were plotted as polysorbate 80 content vs. (b) (4).

The coefficient of determination of the linearity graph was (b) (4), and met the acceptance criteria of (b) (4). The validation report was modified to reflect this change.

- iii. You have evaluated linearity and range from the accuracy results of rVWF drug product samples. Please re-evaluate these characteristics (including linear regression plots) based on the revised accuracy data as requested above, modify your validation report accordingly, and submit for review.

Review of response: The sponsor referred to the regression plots of (b) (4) in section 4.6 of VN-11-04053TB-CVRX3.03. The sponsor's accuracy data was not acceptable because they were obtained using the (b) (4) but not the drug product. Another IR was submitted to the sponsor to re-evaluate range of the assay based on the revised accuracy/linearity and precision data.

- iv. You have studied specificity (section 4.5) by measuring the response of buffer used for the preparation of polysorbate 80 standards. Please provide data obtained by the analysis of representative rVWF product matrix, which contains all components of the drug product except polysorbate 80, to demonstrate the specificity of your method and that the results are not affected by the product matrix.

Review of response: Additional validation data to address the impact of (b) (4), (b) (4), mannitol and trehalose on polysorbate 80 results in the (b) (4) were submitted by the sponsor by updating section 4.5 of the validation report. No interference was observed, and the recovery of polysorbate 80 was in the range of (b) (4). However, the sponsor did not evaluate all the excipients that are present in the drug product. Another IR was submitted.

- v. Please provide data obtained using rVWF drug product to demonstrate that the assay variability is within the acceptable range.

Review of response: As per sponsor's response, the intermediate precision was evaluated with (b) (4) sample, which constitutes an (b) (4). Thus, intermediate precision was not adequately demonstrated for the formulated drug product. An additional IR was submitted to the sponsor.

- vi. You have not submitted the robustness data for your method. Please provide the results to permit complete review of your assay.

Review of response: In response, the sponsor submitted the robustness results obtained by testing polysorbate 80 standards. We had requested data obtained using representative final container samples. Thus, the sponsor's response is not acceptable, and another IR was submitted to the sponsor.

Second Information request: After the review of response to the first IR, a new IR was submitted to the sponsor to address the deficiencies. Baxter responded that a revalidation of the polysorbate 80 assay method is needed and will be able to provide a response by Sept 25, 2015. CBER agreed to the timeline.

We have the following questions/comments regarding the Method validation report and Response to CBER IR received on 22 May 2015:

- a. In response to our previous IR (Question 3-a, sent on 23rd April 2015) in which we had requested linearity/accuracy data in the drug product matrix, you have provided the results obtained by testing (b) (4) sample. As per your manufacturing process description, (b) (4) does not represent the final container sample. Thus, your response is not acceptable. As requested in the previous IR, please provide appropriate linearity/accuracy data using the drug product, and demonstrate parallelism of results between the standard and samples by regression analysis.
- b. As requested in the previous IR question (3-c, sent on 23rd April 2015), please re-evaluate range of the assay based on the revised accuracy, linearity and precision data obtained from representative drug product samples, and modify your validation report.
- c. You have evaluated Intermediate precision with (b) (4) sample, which constitutes an unformulated bulk drug substance according to your manufacturing process description. Thus, you have not demonstrated intermediate precision adequately. As requested in the previous IR, please provide data obtained with your drug product to demonstrate that the method's variability is acceptable.
- d. Please provide data to show specificity of the method based on the analysis of representative product samples and matrix solution/formulation buffer that does not contain polysorbate 80 to demonstrate that the method works for your product and results are not affected by the product matrix.
- e. You have studied robustness by testing polysorbate 80 standards. Please provide data obtained using representative final container samples which address the effect of deliberate variation of critical method parameters.

Conclusion: The method is clearly described. However, there are outstanding issues with the method validation as discussed in the second IR, which need to be addressed.

11. Determination of the Glycine Content in Recombinant rVWF by (b) (4)

The determination of glycine content in rVWF Final Drug Product (FDP) is performed by (b) (4). The proposed specification is (b) (4) after reconstitution for both 650 (5 mL) and 1300 IU/vial (10 mL) formulations.

Method

(b) (4)



(b) (4)

Conclusion: The method is described and validated adequately for the intended use.

12. Determination of Citrate Content in Recombinant rVWF by (b) (4)

Citrate is an excipient used to (b) (4) of the rVWF (b) (4). The proposed specification is (b) (4) after reconstitution for both 650 and 1300 IU/vial formulations.

Method

(b) (4)

(b) (4)

Method Validation

(b) (4)

(b) (4)

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

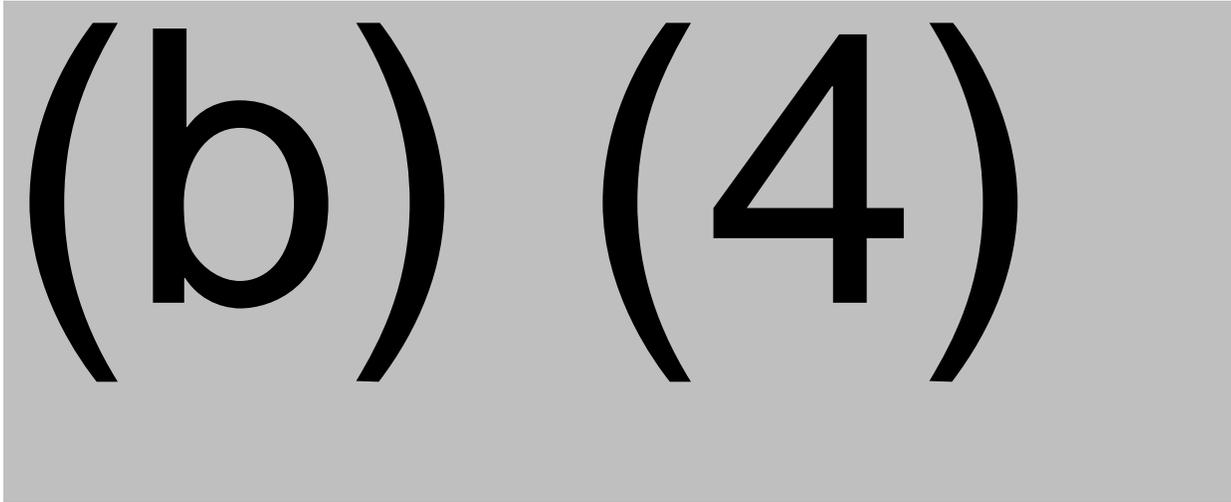
[Redacted]

[Redacted]

[Redacted]

[Redacted]

13. Sodium Content by (b) (4)



Information Request and Review

First Information request: The following IR was submitted to the sponsor on 23 April 2015. The response by Baxter Healthcare Corporation received as Amendment 6 on 22 May 2015, is discussed below.

- i. In the Consolidated Validation Report VN1104082TB-CVRX4.02 located in 3.2.P.5.3 for the Sodium Assay by (b) (4), for determination of specificity, you do not list the (b) (4) used. Please provide a list of the (b) (4) used, their concentration, and their effect on the (b) (4) level.

Review of the Response: (b) (4)



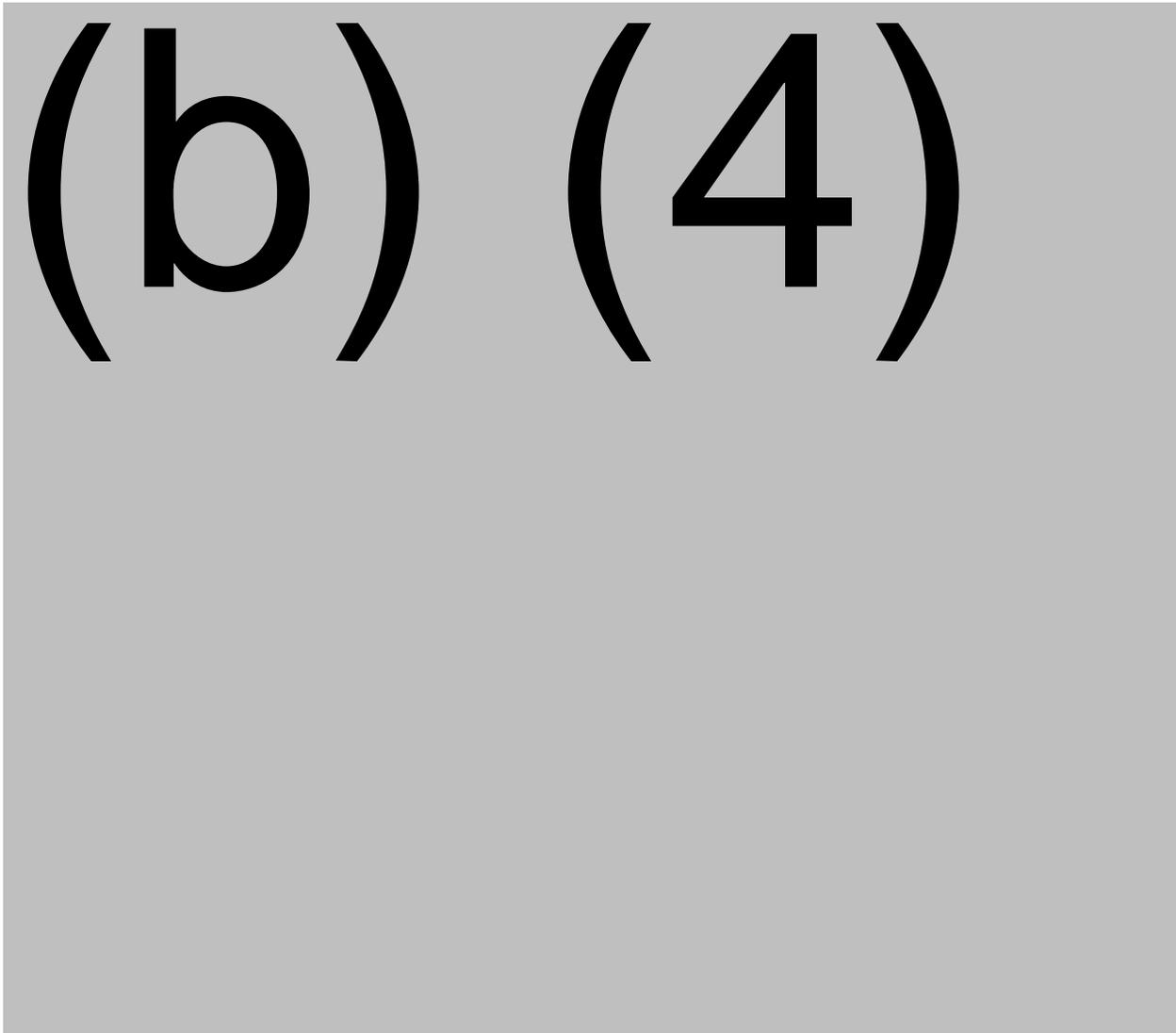
- ii. In the Consolidated Validation Report VN1104082TB-CVRX4.02 located in 3.2.P.5.3 for the Sodium Assay by (b) (4), for determination of robustness, you did not provide the details of the parameters which were varied. Please provide a list of the parameters which were varied and their effect on the Na level.

Review of the Response: The sponsor responded that the following robustness parameters were assessed: (b) (4)

(b) (4) used in the course of performing the assay), (b) (4) (b) (4). No effects on the results of sodium concentrations were observed.

Conclusion: Suitability of the Sodium procedure has been satisfactorily demonstrated for assay of Drug Product samples.

14. pH



16. Appearance of Lyophilized Cake

The specification for appearance of Cake is white to off-white friable powder.

Method

The lyophilized material is visually examined for color and appearance, as described in (b) (4)

[Redacted text block] . Visual inspection is appropriate to verify appearance of the lyophilized cake, and validation of this method is not necessary.

Conclusion: The assay is approvable as a release test for rVWF drug product.

17. Appearance of Reconstituted solution and Reconstitution time

The specification for appearance of Reconstituted solution is clear and colorless solution, free from particles; and for Reconstitution time is (b) (4)

Method

(b) (4)

Conclusion: The assay is approvable as a release test for rVWF drug product.

18. Determination Particulate Matters by (b) (4)

Determination of particulate matter is performed by (b) (4)

The proposed specifications are: (b) (4)
These specifications are consistent with (b) (4)

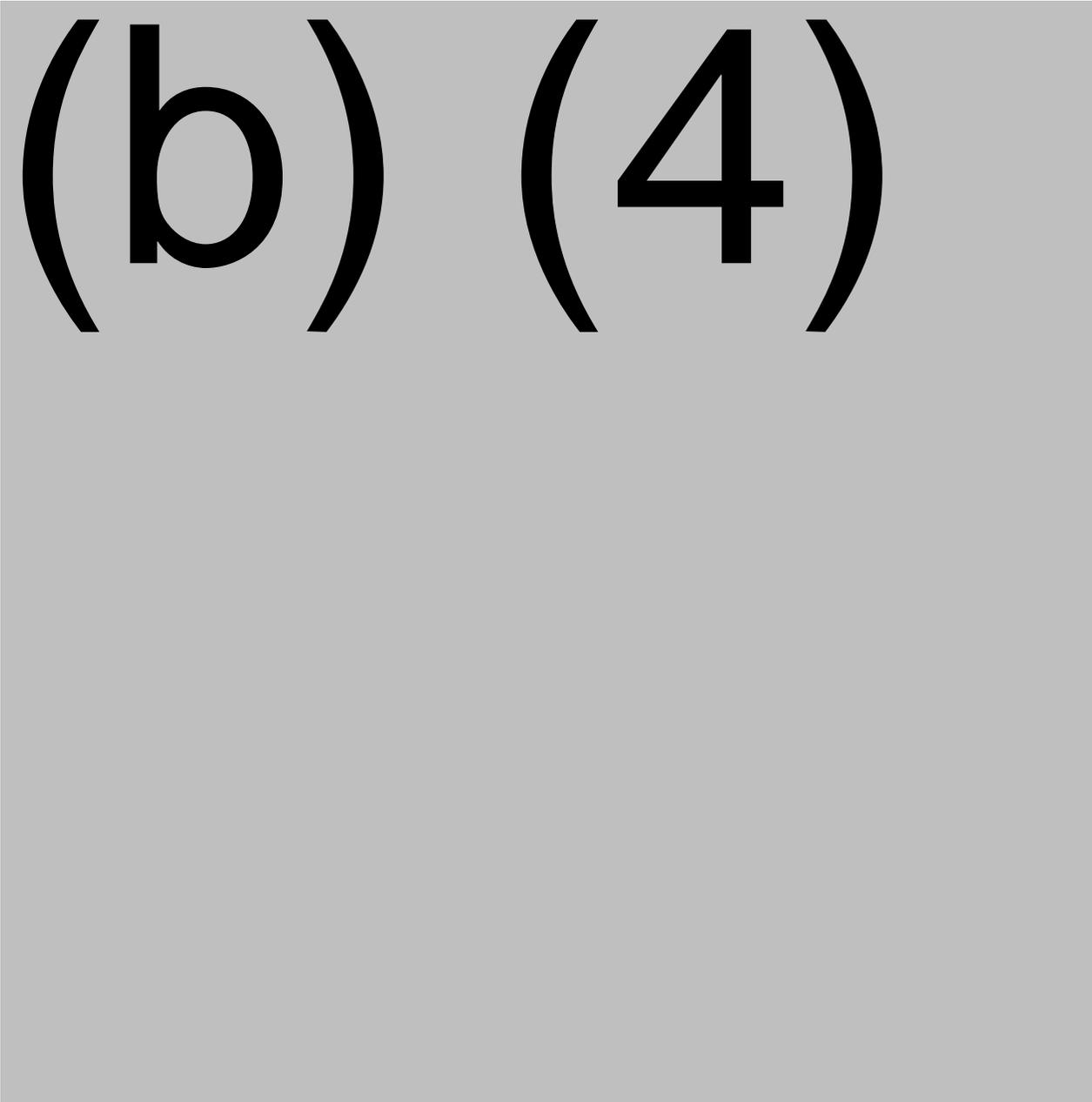
Method

(b) (4)

Method Verification

(b) (4)

Parameter	Acceptance criterion	Result
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(b) (4)

Conclusion: The method and verification were adequate for the intended purpose of quantitating particulate contamination with respect to the specification limits of (b) (4)