



From Parmesh Dutt, DBSQC/OCBQ
Hsiaoling Wang, DBSQC/OCBQ
Ritu Agarwal, DBSQC/OCBQ
Lokesh Bhattacharyya, DBSQC/OCBQ

To STN: #125574/0

Through William M. McCormick, Director, DBSQC/OCBQ

Product Recombinant Antihemophilic Factor (FVIII), Kovaltry (BAY 81-8973)

Sponsor Bayer Corp.

Subject: Final (Addendum) Discipline Review Memo for Biological License
Application for Coagulation Factor VIII (Recombinant), STN: 125574/0
Kovaltry (BAY 81-8973)

Summary of Review

A new BLA was submitted for Coagulation Factor VIII (Recombinant) (STN#125574) by Bayer. This Final (Addendum) memo applies to the review of the outstanding issues of the following analytical methods and their validations, as used for the lot release of the drug product.

1. Factor VIII Potency by Clotting Assay

2. (b) (4)

4. Sucrose content by (b) (4)

All of the outstanding issues have been resolved for the four tests listed above. It is concluded that these methods have been validated adequately and are suitable for use for lot release.

All other quality control test methods and their validations were found to be appropriate for the quality control lot release testing and were validated adequately (Primary Discipline Review memo from DBSQC, dated August 26, 2015).

Background

Kovaltry (BAY 81-8973) Drug Product is a full-length recombinant human coagulation factor VIII (rFVIII) product indicated for use in adults and children with hemophilia A for routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes,

control and prevention of bleeding episodes, peri-operative management (surgical prophylaxis), (b) (4)

and is proposed to be administered intravenously. Kovaltry is proposed to be available as a lyophilized powder in single-use glass vials containing 250, 500, 1000, 2000 and 3000 IU per vial.

The sponsor proposed 14 tests for the quality control lot release of Kovaltry, and submitted either an SOP or detailed descriptions of the test methods and as well as reports of the method validation for the tests. Among them, 10 tests were found to be adequately described and validated, and it was concluded in the Primary Discipline Review (PDR) memo from DBSQC, dated August 26, 2015, these are suitable for lot release. However, there were outstanding issues (Information Requests) for the four methods listed above

Submitted Information Reviewed

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

- 125574/0.17 received on July 15, 2015
 - 1.2 Response to Authority Request Dated June 16, 2015
- 125574/0.19 received on July 31, 2015
 - 2.3.R. Regional Information: Chromogenic Substrate Assay for Release of BAY 81-8973
- 125574/0.21 received on August 6, 2015
 - 1.2 Cover Letters: Response to Info Request (CMC), dated July 23, 2015
- 125574/0.28 received on September 01, 2015
 - 1.2 Response to Authority Request dated August 18, 2015
- 125574/0.28 received on February 08, 2015
 - 1.2 Response to Authority Request dated January 25, 2015
 - 2.3.R. Regional Information: Method Validation Report: (b) (4) of rFVIII-PF Preparations using (b) (4), Val Doc No : MVR-MVBC393-0002.05

Review Narrative

1. Factor VIII Potency by Clotting Assay

This method uses the activated partial thromboplastin time (aPTT) to measure the FVIII potency.

Outstanding Information Requests

The following IR was submitted to the sponsor on 23 July 2015. Review of the response will be included in the Final/Addendum memo.

We reviewed your SOP (Doc. # S-000-BF-069) and the validation report (Doc.# BR-000-BF-069-02.01) for STN: 125574, which you submitted as Amendment 7, and have the following information request.

- a. You measured accuracy of the clotting assay using two different platforms however both methods are One-stage clotting assays. Please provide data for accuracy of the assay by comparing your results using an (b) (4) method or from (b) (4).

Review of the response: The sponsor addressed the question by measuring the potency of the WHO (b) (4) International Standard against (b) (4) different vials of the Kogenate-FS in-house potency standard, (b) (4), using (b) (4). The recovery of the WHO (b) (4) IS was (b) (4). However, this study does not address accuracy of the method because the International Standard is not the drug product. The results demonstrate a verification of the potency of the in-house standard. Furthermore, the sponsor did not address in their response a comparison of their One-Stage Clotting (OS) method to an (b) (4) method. However, we found that in the Chromogenic Assay Method Validation and Report submitted in Amendment 19 gave sufficient information to address the question. A comparison of potency using the FVIII chromogenic (CS) and One-Stage Clotting (OS) assays was carried out in a 2014 study using the Kogenate-FS in-house potency standard, (b) (4), which was calibrated against the WHO (b) (4) IS. (b) (4) lots of drug product manufactured between 2013 and 2014 were tested by the OS assay and were compared to the results obtained by CS assay using the same standard. From these (b) (4) lots, the CS/OS ratios were (b) (4). The data provides adequate information comparing the OS to the (b) (4) CS method to conclude accuracy of the used. No further information is needed to address the IR.

- b. You provided only a brief summary of the data for robustness studies. Please provide actual data for the robustness studies.

Review of the response: The sponsor provided the robustness data addressing the following parameters: (b) (4)

Testing of 3 lots of (b) (4) and 3 different lots of drug product using WHO (b) (4) International Standard gave a maximum difference of (b) (4) in potency value. The drug product was stable from (b) (4) of storage under ambient or instrument's cooler temperatures. The (b) (4) drug product was stable for (b) (4)

concentration to (b) (4) resulted in no significant difference in potency, however the results failed the parallelism acceptance criteria, suggesting the concentration of CaCl_2 should be kept at the nominal value. Different reconstitution volumes of aPTT (b) (4), compared to nominal (b) (4) gave a difference of (b) (4) only compared to control. Finally, testing a different candidate reagent (b) (4) instead of (b) (4)

(b) (4) APTT reagent gave values close to (b) (4). The review of robustness studies concludes that the method is sufficient robust for quantitation of Factor VIII.

Conclusion: The sponsor adequately addressed our IRs. There is no pending issue pertaining to the one-stage clotting assay method validation. The method is adequately validated and suitable for the lot release testing of Kovaltry drug product.

2. (b) (4)

(b) (4)

Outstanding Information Requests

After the review of response to the first IR, a second IR was submitted to the sponsor on 16 June 2015. The response was received on July 17, 2015 as part of Amendment 17.

- a. In our previous IR (dated 4 May 2015, question 2.a.i), we requested you to provide data to show that the (b) (4) of your Antihemophilic Factor (FVIII) protein is not altered due to the presence of (b) (4). You have not provided any data as requested. Please provide data as requested in the previous IR. This is critical because we need to understand that your (b) (4) method truly show (b) (4) of the active protein in your product.

Review of the response: The (b) (4) submitted by the sponsor in the original application and in the first IR did not show any (b) (4). The sponsor designated a 'Region 1', which could be potentially the (b) (4)

Secondly, the sponsor submitted the (b) (4) profile from a (b) (4) experiment, which also shows no (b) (4). However, the sponsor did not provide the run conditions and composition of the eluents used for (b) (4). The primary concern we have is the possibility that (b) (4) present in the eluent of the (b) (4)

The sponsor provided (b) (4) of the FVIII protein from an earlier purification step (b) (4), using the same (b) (4) method, which shows that the (b) (4) establishing that the (b) (4) and has been removed subsequently by the (b) (4) process.

- b. In response to our previous IR (dated 4 May 2015, question 2.a.i), you provided results from an (b) (4) method as an (b) (4) method to show that (b) (4) are either absent or present in your FVIII product below the

detection limit. Please provide the details of operating conditions of the (b) (4), including compositions of the (b) (4).

Review of the response: The sponsor provided details of the operating conditions for (b) (4). Of particular concern is the (b) (4) phase, which was reported to be (b) (4). As discussed above, this addresses the concern this reviewer has regarding the potential for (b) (4) by the presence of (b) (4) in the eluent for (b) (4).

- c. In our previous IR on the method validation report (dated 4 May 2015, question 2.b.i), we requested you to provide data and data analysis to justify that the revised acceptance criteria are adequately set for all instances where you revised the acceptance criteria. You have not provided any data but referred to Protocol Deviation Reports, PDR 001, PDR 002 and PDR 003. We have reviewed these three Protocol Deviation Reports before submitting our IR and found that they have vague and somewhat circular reasoning on why the previously set acceptance criteria are incorrect however did not have data-based justifications on why the new acceptance criteria are correct. Please provide data and data analysis to justify appropriateness of the revised acceptance criteria for validation characteristics where acceptance criteria have been revised. You may disregard any of our previous comment on the validation of Region 1 of your (b) (4) in this context because you have now validated Region 1 differently, in response to our previous IR (dated 4 May 2015). However, we still need data, as requested in question 1.a above, to demonstrate that the (b) (4) are essentially absent in the BAY 81-8973 product.

Review of the response: The sponsor provided examples of calculations for the new acceptance criteria using data from actual runs. The acceptance criteria were widened as Protocol Deviation Reports, PDR 001, PDR 002 and PDR 003, based on the actual data. The explanations and example calculations are satisfactory, however, their calculations show that the results from the (b) (4) method are highly variable, much more than what is expected for a typical (b) (4) method. It is apparent that the sponsor did not understand the variability of the method before conducting the method validation experiments.

- d. In response to our questions 1.a.i and 1.a.ii of our previous IR (dated 4 May 2015), you indicated that the (b) (4) method is (b) (4) to the (b) (4) method. However, in response to our questions 2.b.ii and 2.b.iii, you indicated that there is no appropriate (b) (4) method. Your responses at two places appear to be contradictory. Please explain.

Review of the response: The sponsor explained that they meant (b) (4) in the qualitative sense and not in a quantitative sense. We do not agree that the sponsor has demonstrated that (b) (4) method to be (b) (4), either quantitatively or qualitatively. However, it does not affect the regulatory decision because the primary concern about the (b) (4) that we had was addressed adequately in response to question 'a.' above.

- e. You indicated in your validation report (page 2 of 109), "Accuracy could not be performed per ICH guidelines on Regions 1, 3 and 4 as there are no samples available without any impurities, nor individual regions available for (b) (4)." However, we found methods in the literature to enrich samples of FVIII (b) (4). This may allow you to prepare samples with altered (b) (4) which you may (b) (4) to your BAY 81-8973 drug product to demonstrate method accuracy for different regions of your (b) (4) and LOQ for Region 4. Have you attempted to increase the proportion of (b) (4) in BAY 81-8973 (b) (4) drug product using any of the literature reported methods? Please provide your results with applicable literature reference.

Since the sponsor did not submit response to this IR, the following IR was sent on 25 January 2016. The response was received on 8 February 2016 (Amendment 44).

In amendment dated July 15, 2015 (eCTD sequence 0016) to your BLA for Kovaltry, STN 125574, you committed to conduct further studies for the (b) (4) assay; specifically, for assessing accuracy, linearity and LOQ for Region 4 and possibly Region 1 (page 16 of 23, Response to Question 2e of FDA Information Request dated June 16, 2015). You also indicated that these studies were planned in August 2015. However, we have not received data from this study to this date. Please submit results from the above mentioned study as soon as possible to permit us to complete the review of your BLA for Kovaltry.

Review of the response: The sponsor provided results of evaluation of accuracy, linearity and LOQ for Regions 1 and 4. Samples of 250 IU DP or equivalent were used in this study since they constitute the lowest DP formulation and represent the most stringent conditions.

Region 1 (b) (4): Samples of 250 IU DP were (b) (4). Since this plot actually demonstrates method accuracy but not linearity, we plotted (b) (4), based on the data provided under Linearity/Accuracy Results for Region 1 of the validation report, Doc No. MVR-MV-BC393-0002.05, (the result section of the validation report does not have table number or page number) and found that the correlation coefficient (r^2) to be (b) (4). Since the (b) (4), our calculation provides appropriate estimation of linearity. The (b) (4) recovery is in the range (b) (4). Both results met sponsor's acceptance criteria, (b) (4) and (b) (4) recovery (b) (4), demonstrating accuracy of the method for Region 1. The LOQ calculated from the slope of the plot and residual standard deviation was found to be (b) (4).

Region 4 (b) (4) Samples of (b) (4) was (b) (4) of that of 250 IU DP and are (b) (4) to demonstrate linearity of the method. Since this plot actually demonstrates

method accuracy but not linearity, we plotted (b) (4) against the volume of (b) (4) based on the data provided under Linearity/Accuracy Results for Region 4 of the validation report, Doc No. MVR-MV-BC393-0002.05. Since the (b) (4) volume is proportional to the amount of (b) (4), our calculation provides appropriate estimation of linearity. Our plot (Fig. 1) clearly shows that the level 6 (highest amount of (b) (4)) is outside the linear range of the assay. Considering between level 1 and level 5, corresponding to the (b) (4) solution, shown in Fig. 1, r^2 is (b) (4), which met the acceptance criterion of (b) (4)

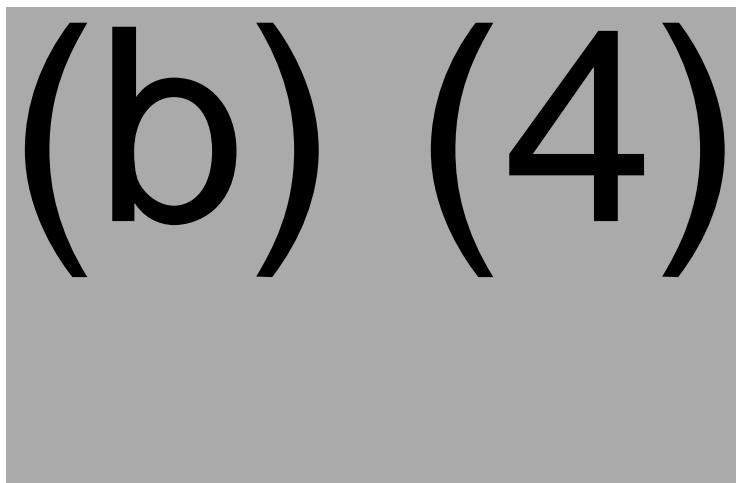


Fig. 1. Plot of Peak area against Volume of (b) (4) solution added

The recovery within this range is (b) (4) which did not meet the acceptance criteria, (b) (4). The (b) (4) which is overestimation in the product, which is acceptable. The LOQ calculated from the slope of the plot (without level 6) and residual standard deviation was found to be (b) (4).

Conclusion: The sponsor adequately addressed our IRs and there is no pending issue pertaining to the (b) (4) assay method validation. The method is adequately validated and suitable for the lot release testing of Kovaltry drug product.

3. Moisture by (b) (4)

(b) (4) is proposed to be the primary method for the determination of residual moisture and the proposed specification is (b) (4)

The specificity study encompassed the ranges of (b) (4) for sucrose and (b) (4) for glycine in the submitted supporting data. No more data was provided to support the specificity evaluation of the effect of the whole range for sucrose (b) (4) and glycine (b) (4) on moisture determination.

Since this quantitative method only used (b) (4) approach, it is considered a relatively weak model in comparison to more frequently used multivariate models. This reviewer strongly suggests that this method be used within the validated ranges and not extrapolated beyond the validated ranges of matrix components due to the complex nature of matrix effects in this method. An alternative solution is that the sponsor may narrow the specification for sucrose to (b) (4) and glycine to (b) (4).

Outstanding Information Request

The outstanding IR regarding (b) (4) assay was sent to sponsor on August 18, 2015. The responses were received on September 01, 2015 as part of Amendment 28.

- a. In the Table 1 of amendment 17, you indicated specifications of glycine and sucrose as (b) (4), respectively. They are inconsistent with the specifications you proposed in the original submission and in amendment 08, which have specifications of these two excipients as (b) (4). Please clarify.

Review of the response: The sponsor informed that they agree to revise their proposed specifications for sucrose and glycine in the drug product as (b) (4) respectively. These specification ranges are consistent with the range in which the model is validated.

Conclusion: The (b) (4) method can be approved for use in the drug product lots that contain sucrose and glycine within (b) (4) respectively.

4. Sucrose content by (b) (4)

The proposed specification is (b) (4) for all drug product strengths (250, 500, 1000, 2000 and 3000 IU/vial of Factor VIII).

Outstanding Information Requests

After the review of response to the first IR, the following IR was submitted to the sponsor on 16 June 2015. The response was received on July 17, 2015 as part of Amendment 17.

- a. In response to our previous IR (dated 4 May 2015, question 4.a.i), you have provided an explanation to support that the data obtained with (b) (4) validation study as representative of drug product samples. We do not agree because your drug product has a matrix different from that of the (b) (4). Please provide linearity and accuracy data using your BAY 81-8973 drug product.

Review of the response: In response, the sponsor explained that the (b) (4) drug product matrix are the same, and there are no differences in polysorbate 80 levels. At the downstream manufacturing (b) (4) step, even though the (b) (4) does not contain polysorbate 80, this analyte is retained during the (b) (4) process. The (b) (4) compared to the drug product, however, the

specificity study demonstrates that the protein does not interfere with the measurement of sucrose, and therefore, the validation data obtained with the (b) (4) presents a worse-case scenario and is adequate for the analysis of drug product. The sponsor re-assessed the linearity/accuracy results. Three linearity runs were performed and the results were averaged to produce the plot of area counts vs. sucrose concentration. The correlation coefficient of the plot was (b) (4), and met the required acceptance criteria (b) (4). The sponsor's response is adequate.

- b. Please provide (b) (4) analysis data for your sucrose (b) (4) from the analysis of the drug product to demonstrate that no other material is coeluting with sucrose (b) (4) to address your method specificity.

Review of response: Additional validation data to address the impact of (b) (4) components and protein on sucrose results were submitted by the sponsor. (b) (4)

(b) (4). The (b) (4) of sucrose was baseline separated from the peak of other components in the (b) (4). The (b) (4) buffer shows no (b) (4) in the window of interest. Furthermore, the sucrose data for 1% sucrose in water or drug product were comparable. Thus, protein and other excipients do not interfere with the sucrose quantitation results.

Conclusion: The method is adequately validated and suitable for the lot release testing of Kovaltry drug product.