DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food & Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

To STN # 125661/0

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Sponsor Bayer HealthCare LLC

Subject: Final Review Memo for Quality Control Lot-release Test Methods for Recombinant Pegylated Human Factor VIII, Damoctocog Alfa Pegol Drug Product

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Summary of Review and Conclusion

On August 30, 2017, a new BLA was submitted for recombinant pegylated human factor VIII, Damoctocog Alfa Pegol, Drug Product (STN 125661) by Bayer healthcare LLC. This document constitutes the final review memo from DBSQC for the following analytical methods and their validations, that are used for quality control lot release of this drug substance and drug product.

Drug Substance

(b) (4)

(b) (4) Drug Product

3. Purity by (b) (4)
4. Quantitation of Sucrose by (b) (4)
5. Quantitation of Histidine and Glycine by (b) (4)
6. Determination of Polysorbate 80 by (b) (4)
7. Quantitation of Sodium and Calcium by (b) (4)
8. Determination of (b) (4)
9. Determination of pH

Drug Product

10. Determination of Uniformity of dosage units
11. Determination of Color and clarity

12. Determination of Particulate Matter
13. Appearance before Reconstitution
14. Appearance after Reconstitution and Reconstitution time

Review of the methods and their validations, led to two information requests (IR's), the first was submitted to the sponsor on 12 December 2017, with responses received on 28 December 2017 and 28 February 2018, as Amendments 12 and 20; and the second submitted to the sponsor on 06 April 2018, with responses received as Amendments 33, 39 and 43 on 20 April 2018, 22 May 2018 and 30 May 2018.

Conclusion

All methods reviewed in this memo have been described and validated adequately, and are suitable for lot-release testing of the product.

Background

Bayer healthcare LLC submitted a new BLA for Damoctocog Alfa Pegol (BAY 94-9027) drug product, a B-domain-deleted recombinant human Factor VIII variant, conjugated to a 60 kDa, branched polyethylene glycol (PEG) at a specific site. The product is indicated for use in previously treated adults and adolescents (12 years and older) with hemophilia A (congenital Factor VIII deficiency) for on-demand treatment and control of bleeding episodes, perioperative management of bleeding and routine prophylaxis, to reduce the frequency of bleeding episodes. The drug product is supplied as lyophilized powder in stoppered glass vials with aluminum over-seal, with sterile water for injection contained in a prefilled syringe and vial adapter to facilitate reconstitution and an intravenous administration set for convenience. The single-use product is available in (b) (4) nominal potency fill sizes (b) (4), 500, 1000, 2000, and 3000 International Units or IU). The FVIII potency of each vial is determined by a chromogenic substrate assay.

Submitted Information and Documents

This is an electronic submission. Information submitted and reviewed in support of this supplement included:

- 125661/0 —1.2 Cover letter dated August 30, 2017
- 125661/0 — 2.3 Quality Overall Summary
- 125661/0 — 3.2.S.4.2. Analytical Procedures, (b) (4)
  - Control Test Procedure: Document 011729715: Determination of (b) (4)
  - Control Test Procedure: Document 012707203: Purity by (b) (4)
  - Control Test Procedure: Document 011729218: Quantitation of Sucrose by (b) (4)
  - Control Test Procedure: Document 011730067: Determination of Polysorbate 80 by (b) (4)

  - Control Test Procedure: Document 011729215: Quantitation of Histidine and Glycine by (b) (4)
  - Control Test Procedure: Document 016136687: (b) (4) for PEG-Maleimide
  - Control Test Procedure: Document 011729713: Quantitation of Calcium by (b) (4)
  - Control Test Procedures: Documents 011729710 and 011729712: Determination of color; pH
- 125661/0 — 3.2.P.5.2. Analytical Procedures, Drug Product
  - Control Test Procedure: Document 011746913: Determination of (b) (4)
  - Control Test Procedure: Document 011746914: Determination of Particulate Matter
  - Control Test Procedure: Document 011746916: Determination of Uniformity of dosage Units
  - Control Test Procedure: Document 012700672: Purity by (b) (4)
  - Control Test Procedure: Document 011767925: Quantitation of Sucrose by (b) (4)
  - Control Test Procedure: Document 011746915: Determination of Polysorbate 80 by (b) (4)
  - Control Test Procedure: Document 011768225: Quantitation of Histidine and Glycine by (b) (4)
  - Control Test Procedure: Document 011746910: Quantitation of Sodium and Calcium by (b) (4)
  - Control Test Procedures: Documents 011747197, 011747198, 011747199: Determination of color and clarity; pH; Appearance before Reconstitution; and Appearance after Reconstitution and Reconstitution time
- 125661/0 — 3.2.S.4.3. Validation of Analytical Procedures, (b) (4)
  - Consolidated Validation Reports for the assays mentioned above (under section 3.2.S.4.2)
- 125661/0 — 3.2.P.5.3. Validation of Analytical Procedures, Drug Product
  - Consolidated Validation Reports for the assays mentioned above (under section 3.2.P.5.2)
- 125661/12 — 1.11.1 Quality Information Amendment; Response to IR dated 12 December 2017; Received 28 December 2017
- 125661/20 — 1.11.1 Quality Information Amendment; Response to IR dated 12 December 2017; Received 28 February 2018
- 125661/33 — 1.11.1 Quality Information Amendment; Response to IR dated 06 April 2018; Received 20 April 2018
- 125661/39 — 1.11.1 Quality Information Amendment; Response to IR dated 06 April 2018; Received 22 May 2018
- 125661/43 — 1.11.1 Quality Information Amendment; Response to IR dated 06 April 2018; Received 30 May 2018

Review Narrative

Drug Substance

(b) (4)

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

(b) (4)

Drug Product

3. Purity by (b) (4)

The proposed specification for purity is (b) (4)

(b) (4) drug product, respectively.

Method

The purity, (b) (4)

The assay validity criteria included the acceptable (b) (4)

Additionally, the results for (b) (4) purity (b) (4) should be within the established range.

Method Validation

The method is validated as a quantitative assay for purity of pegylated rFVIII (Damoctotocog Alfa Pegol) drug product. The following characteristics were evaluated: specificity, linearity, range, accuracy, repeatability, intermediate precision and Robustness.

(b) (4)

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

(b) (4)

First Information request: The following IR was submitted to the sponsor on 12 December 2017. The responses from Bayer received as Amendment 12 on 28 December 2017 and Amendment 20 on 28 February 2018, are discussed below.

A. We have the following questions/comments regarding the Method validation report, Document number 012701193.

   i. In the data presented in section 3.1.1, you have determined accuracy based on (b) (4) . (a) Please provide the description and lot numbers of drug product samples that were used for accuracy validation. (b) Please explain how you have obtained (b) (4) (c) Please clarify how you calculated the (b) (4) . (d) You have not evaluated the (b) (4) . Please provide results from a (b) (4) , to demonstrate accuracy of your assay.

   Review of response: (a) The sponsor stated that the (b) (4) , lot (b) (4) , was used to prepare samples for assessing assay linearity. (b) The (b) (4) was calculated based on the (b) (4) (c) The (b) (4) was calculated in terms of (b) (4) (d) In Amendment 20, the sponsor provided the accuracy data to cover the specified (b) (4) The sponsor did not provide the data for (b) (4) for the above accuracy study, hence another IR was submitted to the sponsor.

ii. Please provide (b) (4) in the linearity study (section 3.1.1) of your validation report.

Review of response: As requested by CBER, the sponsor provided the linearity (b) (4) of the data submitted in the original submission. The (b) (4) . Thus, linearity of the assay was sufficiently demonstrated.

iii. Regarding sections 3.2 and 3.3, Precision: please submit complete data set and include the results for (b) (4) (b) (4) for the evaluation of repeatability and intermediate precision.

Review of response: In response, the sponsor submitted the revised validation report. The data obtained in repeatability and intermediate precision studies is summarized in the review section above.

Second Information request: The following IR was submitted to the sponsor on 06 April 2018. The responses by Bayer received as Amendment 33 on 20 April 2018, is discussed below.

A. Section 6.1 of document number 012700672 includes the assay validity criteria based on the (b) (4). Please provide the description and qualification report of the (b) (4) currently in use.

Review of response: In response, the sponsor provided the data that were used to set the acceptance criteria for the (b) (4) . A total of (b) (4) results were included in the analysis. For (b) (4)

B. We have the following question/comment regarding the Method validation report, Document number 012701193: In response to our previous IR question (dated 12 December 2017), you provided data with evaluation of accuracy based on the (b) (4) . Please provide the results obtained for (b) (4) analyzed for the accuracy study. Please ensure that the data covers (b) (4)

Review of response: In response to the IR, the sponsor submitted additional accuracy data to cover the specified (b) (4)

(b) (4)

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Conclusion: The method is clearly described and validated, and is acceptable as a lot-release test for determination of purity of Damoctocog Alfa Pegol drug (b) (4) /product.

4. Quantitation of Sucrose by (b) (4)

Sucrose is an excipient in Damoctocog Alfa Pegol drug product. The sample matrices (excipients) are similar in Damoctocog Alfa Pegol (b) (4) drug product samples. The drug (b) (4) /product specification for sucrose is (b) (4) for all formulations.

Method

The sucrose concentration in the Damoctocog Alfa Pegol (b) (4) /product is determined by (b) (4) following the procedure described in Document 0011767925. The method is identical to the method for the determination of sucrose in recombinant coagulation factor VIII drug product (Kogenate, STN 103332) that was submitted by the same sponsor, including the assay validity criteria.

Method Validation

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

The method was previously validated for the analysis of Bayer's BAY 81-8973 recombinant coagulation factor VIII drug product, Kogenate, which was approved, and the sponsor has submitted the same validation for the current submission. The drug product formulations of BAY 81-8973 and Damoctocog Alfa Pegol are (b) (4), except for the differences in (b) (4) . Further, the excipient composition is also (b) (4) (b) (4) Damoctocog Alfa Pegol (b) (4) drug product samples. As per the sponsor, the validation for BAY 81-8973 (Kogenate) would be applicable to (b) (4) Damoctocog Alfa Pegol (b) (4) drug product due to similar formulations. We agree with sponsor's position except that they should show method specificity for Damoctocog Alfa Pegol. An IR was submitted.

The validation characteristics evaluated using (b) (4) (BAY 81-8973, and after responses to CBER IR's are summarized in the table 1.

Table 1: Assay for Sucrose by (b) (4) - Validation Summary

(b) (4)

First Information request: The following IR was submitted to the sponsor on 12 December 2017. The response by Bayer received as Amendment 12 on 28 December 2017, is discussed below.

A. Regarding your testing instruction for 'Sucrose Assay', document number 011767925: (i) please provide the composition, and the qualification report of the current control sample that is used to assess the validity of sucrose assay, (ii) please provide the description of sucrose reference standard, (iii) For (b) (4), please include a specification for (b) (4) sucrose (b) (4) based on your historical results.

Review of response: (i) In response, the sponsor informed that the assay (b) (4)

(ii) According to the sponsor, the sucrose (b) (4) . No further information is required.

(iii) The test method requires that the sucrose (b) (4)

B. We have the following questions/comments regarding the Method validation report, Document number 011749015.

i. You have demonstrated specificity of the assay using BAY 81-8973, and you propose that due to similarity in drug product matrices, the method can be applied to Damoctocog Alfa Pegol, even though this product has a different (b) (4) . We do not agree. Please provide the data and (b) (4) obtained with (b) (4) /product, (b) (4) , and a comparison of (b) (4) of sucrose in drug product with that of sucrose (b) (4) , to establish the specificity of the assay.

Review of response: In response to CBER IR, the sponsor provided additional specificity data obtained from sucrose (b) (4) , Damoctocog Alfa Pegol product, and BAY 81-8973 product. The (b) (4) for the sucrose (b) (4) in both the (b) (4) Damoctocog Alfa Pegol product (b) (4) in the BAY 81-8973 (Kogenate, STN 103332) product sample, and was comparable to the (b) (4) obtained with the sucrose (b) (4) These results indicate that the difference in (b) (4) of two drug products (Damoctocog Alfa Pegol product and BAY 81-8973) do not interfere with the quantitation of sucrose. Hence due to similar formulations, the validation for BAY 81-8973 can be considered as appropriate for use for Damoctocog Alfa Pegol product.

Conclusion: The method is adequately described and validated, and is acceptable as a lot-release test for the determination of sucrose content in Damoctocog Alfa Pegol drug (b) (4) /product.

5. Quantitation of Histidine and Glycine by (b) (4)

Histidine and Glycine are excipients in Damoctocog Alfa Pegol drug product. The matrices of Damoctocog Alfa Pegol (b) (4) drug product are similar to Kogenate product (STN 103332). The specifications for histidine are (b) (4) drug product, respectively. The specifications for glycine are (b) (4) product.

Method

The concentration of histidine and glycine in (b) (4) drug product is determined by (b) (4) , following the procedure described in document 011768226. In this method, the (b) (4) . The method is identical to the method for the determination of histidine/glycine in (b) (4) coagulation factor VIII drug product (Kogenate, STN 103332).

Method Validation

The method is used as a quantitative determination of histidine and glycine in the (b) (4) drug product.

The method was previously validated for the analysis of Bayer's BAY 81-8973 recombinant coagulation factor VIII drug product, and the sponsor has submitted the same validation for the current submission. The following validation characteristics were evaluated: specificity, linearity, range, accuracy, repeatability and intermediate precision. The drug product formulations of BAY 81-8973 (Kogenate, STN 103332) and Damoctocog Alfa Pegol (b) (4) , with the exception of differences in (b) (4) .

The validation for BAY 81-8973 (Kogenate) would be applicable to (b) (4) Damoctocog Alfa Pegol (b) (4) drug product due to similar formulations. We agree with sponsor's position except that they should show method specificity for Damoctocog Alfa Pegol. An IR was submitted. The validation characteristics evaluated using (b) (4) product (BAY 81-8973), and after responses to CBER IR's are summarized in Table 2 below.

Table 2: Assay for Histidine and Glycine by (b) (4) - Validation Summary

(b) (4)

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

(b) (4)

First Information request: The following IR was submitted to the sponsor on 12 December 2017. The responses by Bayer received as Amendment 12 on 28 December 2017 and Amendment 20 on 28 February 2018, are discussed below.

A. Regarding your testing instruction for 'Glycine and histidine Assay', document number 011768226: (i) please provide the composition and qualification details of the control sample mentioned in section 3.0, (ii) please provide the description of glycine and histidine reference standards, (iii) For (b) (4) .

Review of response: (i) The sponsor stated that the (b) (4) . (ii) As per the sponsor, the glycine and histidine (b) (4) (iii) and (iv) The sponsor submitted the updated SOP that included the (b) (4) histidine and glycine (b) (4).

B. We have the following questions/comments regarding the Method validation report, Document number 011748719.

i. You have evaluated specificity of the assay using BAY 81-8973, and you propose that due to similarity in drug product matrices, the method can be applied to Damoctocog Alfa Pegol, even though this product has a different (b) (4) . We do not agree. Please provide the data and (b) (4) obtained with (b) (4) /product, (b) (4) histidine and glycine) in drug product with that of (b) (4) to establish specificity of your assay.

Review of response: In response, the sponsor submitted the (b) (4) histidine and glycine), BAY 81-8973 (Kogenate, STN 103332) and Damoctocog Alfa Pegol product. The (b) (4) of histidine and glycine in (b) (4) However, the sponsor did not submit the (b) (4) . Another IR was sent to the sponsor to provide the required data to demonstrate specificity of the assay.

Second Information request: The following IR was submitted to the sponsor on 06 April 2018. The response by Bayer received as Amendment 33 on 20 April 2018, is discussed below.

A. In our previous IR (dated 12 December 2017) we requested you to include (b) (4) criteria for (b) (4) between glycine and histidine (b) (4) We received your updated SOP. However, you did not provide the data and data analysis to justify the new (b) (4) criteria. Please provide your results in support of this change.

Review of response: In response, the sponsor provided the data that was analyzed to set the criteria for (b) (4) . The updated SOP is acceptable.

B. We have the following question/comment regarding the Method validation report, Document number 011748719: Please provide the (b) (4)

Review of response: In response to CBER IR, the sponsor provided additional specificity data obtained from histidine and glycine (b) (4) glycine or histidine (b) (4) . Therefore, the assay is specific for histidine and glycine.

Conclusion: The method is adequately described and validated, and is acceptable as a lot-release test for determination of histidine and glycine contents in Damoctocog Alfa Pegol drug (b) (4) /product.

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

Polysorbate 80 is an excipient in Damoctocog Alfa Pegol drug product. The sample matrices (excipients) are similar in Damoctocog Alfa Pegol (b) (4) drug product samples. The

drug product specification for polysorbate 80 is based on (b) (4) /product formulations.

Method

The polysorbate 80 concentration in the drug product is determined by a (b) (4) method as described in Document 011828903.(b) (4) polysorbate 80 (b) (4) The method is identical to the method for the determination of polysorbate 80 in (b) (4) recombinant coagulation factor VIII drug product (Kogenate, STN 103332).

Method Validation

The method is used as a quantitative assay for the determination of polysorbate 80 in drug (b) (4) product. The following validation characteristics were evaluated: specificity, linearity, range, accuracy, repeatability and intermediate precision.

The method was previously validated for the analysis of Bayer's BAY 81-8973 recombinant coagulation factor VIII drug product (Kogenate, STN 103332). The validation of the method was approved. Due to similar formulation of BAY 81-8973 and Damoctocog Alfa Pegol drug (b) (4) /drug product, the sponsor has submitted the same validation for the current submission. We agree with sponsor's position except that they should show method specificity for Damoctocog Alfa Pegol. An IR was submitted. The validation characteristics evaluated using the corresponding (b) (4) product (BAY 81-8973), and after responses to CBER IR's are summarized in Table 3 below.

The (b) (4)

Table 3: Assay for Polysorbate 80 - Validation Summary

(b) (4)

(b) (4)

First Information request: The following IR was submitted to the sponsor on 12 December 2017. The response by Bayer received as Amendment 28 on 28 December 2017, is discussed below.

A. With reference to your original BLA section 3.2.P.5.3, for analytical assays for Polysorbate 80 (document #011828903), Sodium and calcium (document #011828905), (b) (4) (document #011828761), Color and clarity (document #011828756) and (b) (4) (document #011828902), you have presented the data obtained with BAY 81-8973. Since the

active component of the drug product associated with the current submission, Damoctocog Alfa Pegol, is significantly different from BAY 81-8973, we cannot conclude that these methods are appropriately validated. Please provide the evaluation of validation characteristics for the above assays using Damoctocog Alfa Pegol.

Review of response: According to the sponsor, the excipient composition of BAY 81-8973 (STN 103332) and Damoctocog Alfa Pegol are very similar. Further, although the active components (proteins) and their concentration is different in the two products, the polysorbate 80 concentration (b) (4) . Therefore, the method specifically measures polysorbate 80 concentration in (b) (4) , and the validation for BAY 81-8973 is applicable to Damoctocog Alfa Pegol. The response is acceptable however, a second IR is necessary to address deficiencies in method validation submitted for BAY 81-8973 (Kogenate, STN 103332).

Second Information request: The following IR was submitted to the sponsor on 06 April 2018. The response by Bayer received as Amendments 33 and 39, on 20 April 2018 and 22 May 2018 are discussed below.

A. Please provide data obtained from drug product (b) (4) polysorbate 80) to substantiate your conclusion that the method is specific.

Review of response: The sponsor provided additional validation data using (b) (4) polysorbate 80. Specificity was assessed by (b) (4) polysorbate 80. (b) (4) polysorbate 80 (b) (4) polysorbate 80 (b) (4) Thus, the method is specific.

Conclusion: The method is adequately described and validated, and is acceptable as a lot-release test for the determination of polysorbate 80 content in Damoctocog Alfa Pegol drug (b) (4) /product.

7. Sodium and Calcium by (b) (4)

The specification for sodium in Damoctocog Alfa Pegol drug product is (b) (4) The specification for calcium is (b) (4) drug product formulations respectively.

Method

The concentration of sodium in drug product, and calcium in drug (b) (4) /product is determined by (b) (4)

(b) (4) . The method is identical to the method for the determination of sodium/calcium in non-pegylated recombinant coagulation factor VIII drug product (STN 103332).

Method Validation

The method is used as a quantitative test for sodium in Damoctocog Alfa Pegol drug (b) (4) /product. The following validation characteristics were evaluated: specificity, linearity, accuracy, repeatability and intermediate precision.

The method was previously validated BAY 81-8973 recombinant coagulation factor VIII drug product. The validation of the method was approved. Due to similar formulation of BAY 81-8973 (Kogenate, STN 103332), the sponsor has submitted the same validation for the current submission. The drug product formulations of Kogenate and Damoctocog Alfa Pegol (b) (4) , except for the differences in (b) (4) Further, the sample matrices (excipients) are also similar in Damoctocog Alfa Pegol (b) (4) drug product samples. According to the sponsor due to similar formulations, the validation for BAY 81-8973 would be applicable to (b) (4) Damoctocog Alfa Pegol (b) (4) drug product. However, since the two drug products are significantly different, we cannot conclude that the method has been validated appropriately for its intended use, and hence an IR was sent to the sponsor.

First Information request: The following IR was submitted to the sponsor on 12 December 2017. The response by Bayer received as Amendment 28 on 28 December 2017, is discussed below.

A. With reference to your original BLA section 3.2.P.5.3, for analytical assays for Polysorbate 80 (document #011828903), Sodium and calcium (document #011828905), (b) (4) (document #011828761), Color and clarity (document #011828756) and (b) (4) (document #011828902), you have presented the data obtained with BAY 81-8973. Since the (b) (4) drug product associated with the current submission, Damoctocog Alfa Pegol, is significantly different from BAY 81-8973, we cannot conclude that these methods are appropriately validated. Please provide the evaluation of validation characteristics for the above assays using Damoctocog Alfa Pegol.

Review of response: According to the sponsor, since the excipient composition of Kogenate and Damoctocog Alfa Pegol (b) (4) , the validation for BAY 81-8973 is applicable to Damoctocog Alfa Pegol. We do not agree with the sponsor. The (b) (4)

(b) (4) sodium and calcium. Thus, another IR was generated for the sponsor to evaluate validation characteristics using Damoctocog Alfa Pegol.

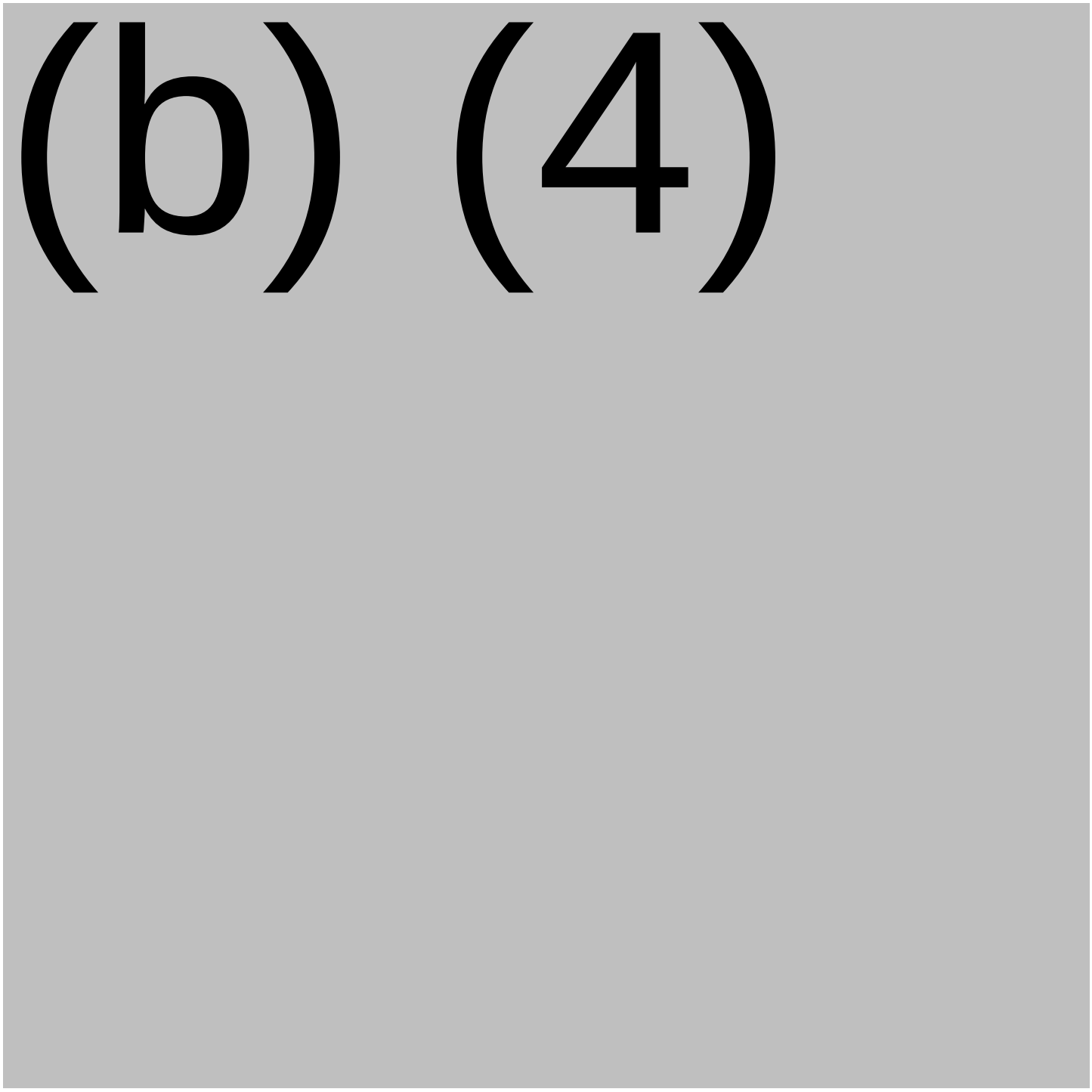
Second Information request: The following IR was submitted to the sponsor on 06 April 2018. The response by Bayer received as Amendment 43 on 30 May 2018, is discussed below.

A. In our previous IR (dated 12 December 2017) on method validation report, we requested you to submit data using the drug product associated with the current submission. You have not provided the requested data to permit the complete review of this assay. Please evaluate the validation characteristics using Damoctocog Alfa Pegol for the assay.

Review of response: The sponsor submitted the required validation data as Amendment 43, on 30 May 2018. The validation characteristics were evaluated using Damoctocog Alfa Pegol. The results are summarized in Table 4 below.

Table 4: Summary of Validation Results for Calcium and Sodium Method using Damoctocog Alfa Pegol

(b) (4)



Conclusion: The method is clearly described and can be approved for quality control lot release testing.

Determination of (b) (4)

[redacted]

9. pH

The pH specification for Damoctocog Alfa Pegol (b) (4) /product is 6.6-7.0.

Method

The pH of the (b) (4) pH determination and is identical to the method for the determination of pH in non-pegylated recombinant coagulation factor VIII drug product (Kogenate, STN 103332).

The measurement of pH is a widely used method, and is dependent (b) (4) Hence, no validation should be necessary.

Conclusion

This is a well-established method. Further information is not required. The assay is approvable as a release test for Damoctocog Alfa Pegol drug (b) (4) product.

Drug Product

10. Determination of Uniformity of Dosage Units

The specification for Damoctocog Alfa Pegol product complies with (b) (4)

Method

The uniformity of dosage unit is determined by (b) (4)

However, in the initial submission, the details of the procedure were not clear. In addition, the verification data submitted were obtained using another FVIII product, not Damoctocog Alfa Pegol drug product. Hence an IR was submitted.

First Information request: The following IR was submitted to the sponsor on 12 December 2017. The response by Bayer received as Amendment 12 on 28 December 2017, is discussed below.

A. It is not clear how you calculated the results of Uniformity of dosage for BAY 81-8973 and Antihemophilic factor (document #011828904). Further, these results do not support the use of this method for Damoctocog Alfa Pegol samples, due to significant differences in the (b) (4) between BAY 81-8973 and Damoctocog Alfa Pegol. Please provide complete verification results, including the raw data and calculations using Damoctocog Alfa Pegol.

Review of response: In response, the sponsor submitted the verification data using Damoctocog Alfa Pegol. As per the submitted data, (b) (4) . The acceptance value for (b) (4) , and within the acceptable range of (b) (4) .

The results indicate that the method is suitable for determining the (b) (4) of the lyophilized product.

Conclusion: The assay is approvable as a release test for Damoctocog Alfa Pegol drug product.

11. Determination of Color and Clarity

The specification for clarity of final product is minimum (b) (4). The release specification for color is maximum (b) (4).

Method

The clarity assay is based on the (b) (4)

Validation

The method was previously validated for the analysis of Bayer's BAY 81-8973 (Kogenate, STN 103332) recombinant coagulation factor VIII drug product, and the sponsor has submitted the same validation for the current submission. Due to similarity between formulation of BAY 81-8973 (Kogenate, STN 103332) and Damoctocog Alfa Pegol, this is acceptable.

Conclusion: The assay is approvable as a release test for Damoctocog Alfa Pegol drug product.

12. Determination of Particulate Matter

The specification for particulate matter (b) (4) for Damoctocog Alfa Pegol drug product is (b) (4).

Method

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

Verification

The sponsor submitted a (b) (4)

Conclusion: The assay is approvable as a release test for Damoctocog Alfa Pegol drug product.

13. Appearance before reconstitution

The specification for appearance of Damoctocog Alfa Pegol product is white to slightly yellow solid.

Method

The lyophilized material is visually examined for color, as described in (b) (4) . Visual inspection is appropriate to verify appearance of lyophilized product, and validation of this method is not necessary.

Conclusion: The assay is approvable as a release test for Damoctocog Alfa Pegol drug product.

14. Appearance after Reconstitution and Reconstitution (Solubility) time

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

Method

The lyophilized material is (b) (4)).
Appearance of reconstituted product is in accordance with (b) (4) . Visual inspection is appropriate to verify the solubility and appearance of solution, and validation of this method is not necessary.

Conclusion: The assay is approvable as a release test for Damoctocog Alfa Pegol drug product.