DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

From: Hsiaoling Wang, Ph.D.
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Laboratory of Analytical Chemistry and Blood Related Products (LACBRP)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: Biologics License Application Submission Tracking Number 125661/0

Subject: Primary Review Memo for Chemical Assays for Jivi [Antihemophilic Factor (recombinant), PEGylated]

Through: Lokesh Bhattacharyya, Ph.D., Lab Chief, CBER/OCBQ/DBSQC

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Applicant: Bayer Healthcare Pharmaceuticals Inc.

Submission Received by CBER: Aug. 30, 2017

Summary:

A new BLA (STN 125661) was submitted by Bayer Healthcare for Jivi [Antihemophilic Factor (recombinant), PEGylated] for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for on-demanding treatment and control of bleeding episodes, perioperative management of bleeding and routine prophylaxis to reduce the frequency of bleeding episodes.

This document constitutes the Primary Review Memo from DBSQC for the following analytical methods and their validations, which are proposed to be used for quality control of the drug substance (DS) and drug product (DP).

1. Quantitation of Moisture by (b) (4) (for DP)
2. (b) (4)
3. (b) (4) Total Protein (b) (4) DP)

This reviewer found that these three analytical procedures were adequately described and validated for their intended uses.

Background

Jivi is lyophilized powder that is intended for intravenous injection following reconstitution with sterile Water for Injection (sWFI). It is supplied in five dosage forms containing (b) (4) 500, 1000, 2000 and 3000 International Units (IU) along with syringes filled with 2.5 mL sWFI.

Documents Reviewed

Original submission STN 125661/0 dated Aug. 30, 2017

- Cover letter
- 2.2 Introduction
- 3.2.S.3.1 Elucidation of Structure and Other Characteristics
- 3.2.S.3.2 Impurities
- 3.2.S.4.1 Specifications of drug substance
- 3.2.S.4.2 Test procedures for drug substance
- 3.2.S.4.4 Batch analyses (drug substance)
- 3.2.S.4.5 Reference standard
- 3.2.P.5.1 Specifications of drug product
- 3.2.P.5.2 Test procedures for drug product
- 3.2.P.5.4 Batch analyses (drug product)
- Test Procedure (P.5.2.72-01): Method for Quantitation of Moisture (b) (4))
- Validation of Test Methods (P.5.3.08-01): Method for Quantitation of Moisture (b) (4)
- Test Procedure (S.4.2.81-01): Method for (b) (4)
- Validation of Test Methods (S.4.3.81-01): Method for (b) (4)
- Test Procedure (P.5.2.61-01): Method for (b) (4)
- Test Procedure (S.4.2.81-01): Method for (b) (4)
- Validation of Test Methods (P.5.3.67-02): Method for (b) (4)
- Validation of Test Methods (S.4.3.81-01): Method for (b) (4)

Amendment 8, dated Dec. 1, 2017

- Response to Authority Request 17Nov2017
- Updated Test Procedure (P.5.2.72-02): Method for Quantitation of Moisture ((b) (4)
- Batch-Related Raw Data (S.4.4.10-01): (b) (4)

Amendment 14, dated Jan. 31, 2018

- Responses to Authority Requests17Nov2017 and 20Nov2017
- Method Validation (MVR-MQ-BC-443-0002.03): Damoctocog Alfa Pegol Method for (b) (4)
- Updated Method Validation (MVR-MQ-BC-443-0002.08): Damoctocog alfa pegol Method for (b) (4)
- Validation of Test Methods (P.5.3.61-02): Method for (b) (4)
- Validation of Test Methods (S.4.3.81-02): Method for (b) (4)

Amendment 24, dated March 19, 2018
- Response to Authority Request 05Mar2018

Amendment 34, dated April 24, 2018
- Response to Authority Request 05Apr2018
- Updated Test Procedure (P.5.2.72-03): Method for Quantitation of Moisture (b) (4)
- Updated Validation Report (P.5.3.08-02): Method for Quantitation of Moisture (b) (4)
- Addendum to Method Validation report: Moisture Content in Lyophilized Products by (b) (4)

Amendment 38, dated May 14, 2018
- Response to Authority Requests dates 05 and 06Apr2018
- Updated Test Procedure (P.5.3.61-03): Method for (b) (4)
- Validation of Test Methods (P.5.3.61-02): Method for (b) (4)
- Validation of Test Methods (S.4.3.81-03): Method for (b) (4)

Review Narrative

1. Quantitation of Moisture in the Drug Product by the (b) (4) method

Method

(b) (4)

The specification of residual moisture for DP is (b) (4).

Method validation

As a quantitative method, the following validation characteristics were evaluated for the validation of the (b) (4) assay: accuracy, precision, linearity, range and robustness.

(b) (4)

(b) (4)

Information request and Review of Response

The following IRs were sent to the sponsor on Nov. 17, 2017. The responses were received on Dec. 1, 2017 in the Amendment 8.

a. We were unable to follow the calculations in section 7 of the test procedure. Please provide an example with details of your calculations from your DP test results.

Review of the response: A detailed calculation is provided with an example in the response. Test procedure was updated with calculation formula. But it appears that there is an error in the calculation formula. A second IR was sent.

b. Please justify wide acceptance criterion of (b) (4) in linearity evaluation in section 3.4.2 of the validation report.

Review of the response: The sponsor agreed that the set acceptance criterion for (b) (4) was wide but pointed out that the actual (b) (4) from the linearity study was (b) (4). The response is adequate.

c. You have determined that the range of the assay to be (b) (4) Please convert it to a reportable value (moisture percent) of your lyophilized product.

Review of the response: The sponsor revised the range to be (b) (4) residual moisture based on the average (b) (4) . The response is acceptable.

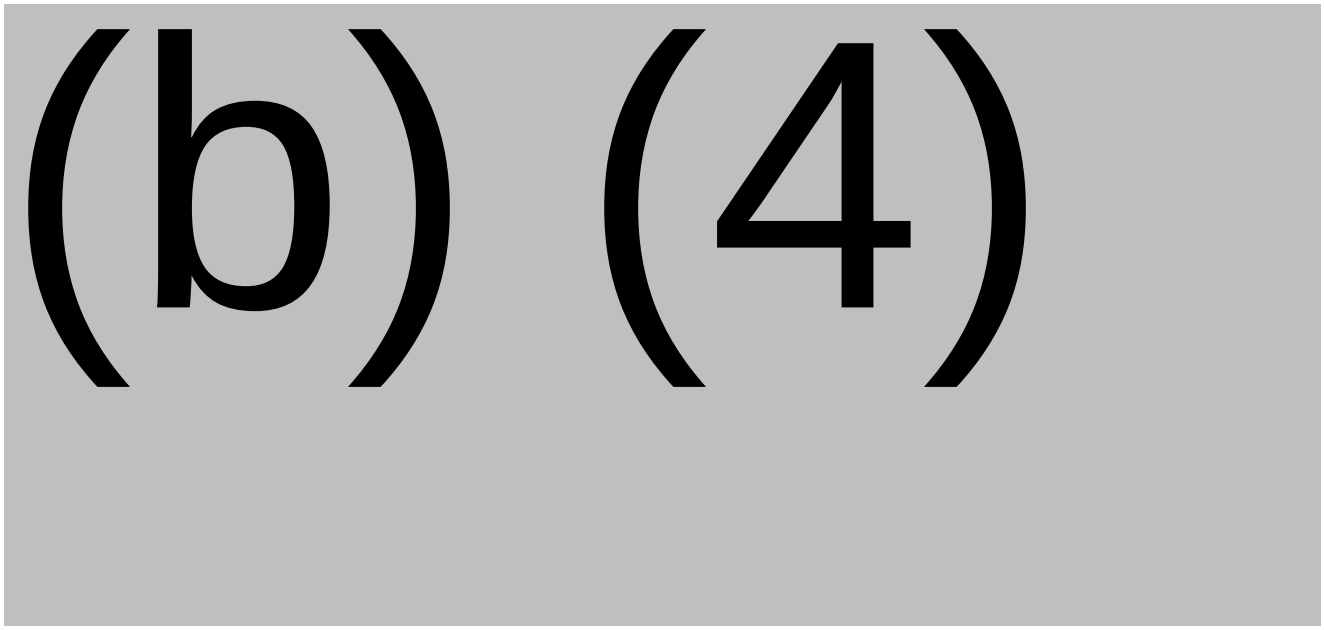
The following IR was sent to sponsor on March 5, 2018. The response was received on March 19, 2018 in the Amendment 24.

The calculation you provided in response to our previous IR 1a (Dated Dec. 1, 2017) is not clear to us. It appears that (b) (4) is not included in the reconstituted (b) (4) . Please clarify your calculation by providing us the equation with clear explanation of the terms used in the equation.

Review of the response: The calculation was explained with example again in the response. FDA reviewer concluded that there is an error in the calculation. The FDA asked the sponsor to make the correction in the 3rd IR.

The 3rd IR regarding the moisture assay was sent to the sponsor on April 5, 2018. The response was received on April 24, 2018 in the Amendment 34.

As we pointed out in our previous information request (dated March 5, 2018), there is an error in the calculation for moisture assay (P.5.2.72#011746912). The table below shows the correct formula for the calculation of $\%H_2O$ and the one you used in the amendment 24 (dated 3/19/2018). You have made an inappropriate subtraction (b) (4) from total water content measured in your formula. Consequently, your calculations have resulted in a small underestimation of the moisture value (see an example in the table below).



Please make necessary corrections in your SOP and validation report and submit both documents for review.

Review of the response: Both the test procedure and validation report were updated after correction of calculation formula. The results for all validation characteristics did not change significantly after recalculation and are acceptable. The response is satisfactory.

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

2. (b) (4) Identity

Method

(b) (4)

Validation

(b) (4)
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(b) (4)

Information Request (IR) and Review of Response

The following IRs were sent to the sponsor on Nov. 17, 2017. The responses were received on Dec. 1, 2017 in the Amendment 8.

a. Please provide rationale of selecting (b) (4) rather than using other (b) (4)

Review of the response: The sponsor explained that (b) (4) A IR was sent later for such explanation.

b. Please provide (b) (4) samples with those of reference standards in your batch analysis (3.4.S.4.4.01-03) tables 1-3, 1-5 and 1-7.

Review of the response: The requested (b) (4) were provided. The difference between

sample and reference standard was (b) (4) lots and considered to have good consistency for (b) (4). The response is satisfactory.

The 2nd IRs were sent on March 5, 2018 and the responses were received on March 19, 2018 in Amendment 24.

a. (b) (4)

Review of the response
The sponsor indicated that the purpose of this assay is to confirm the identity of Damoctocog alfa pegol compared to other recombinant FVIII products produced in the same commercial facility. It is not used for (b) (4) monitoring. There was also a technique issue that the sponsor was not able to use the (b) (4), the response is acceptable.

b. In the response to our Nov.17, 2017 information request 2a (Dated Dec. 1, 2017), you stated that (b) (4) such as (b) (4). Please provide the root cause of this phenomenon.

Review of the response: (b) (4) The response is acceptable.

Conclusion: The test procedure of (b) (4) is adequately described and validated for (b) (4) identification.

3. (b) (4), Total Protein and Specific Activity for (b) (4) DP

Method

(b) (4)

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

(b) (4)

Information Request (IR) and Review of Response

The following IRs were sent to sponsor on Nov. 17, 2017 regarding the validation report. The responses were received on Dec. 1, 2017 in the Amendment 8 and Jan. 31, 2018 in the Amendment 14.

a. In the validation report, you only provide a statistical summary of the data. Please provide the details of experimental results of (b) (4) together with the sample preparation procedure.

Review of the response: The sponsor indicated that the details were submitted as a validation report MVR-MQ-BC-443-0002.03 in section 3.2.R. Regional Information. The response is acceptable.

b. Please provide (b) (4) together with (b) (4) .

Review of the response: The requested (b) (4) was provided. Results are summarized under Validation above. The response is satisfactory.

c. Please provide plots (b) (4)

Review of the response: The requested (b) (4) was provided. Results are discussed under Validation above. The response is satisfactory.

d. Please provide (b) (4) determination in the validation report.

Review of the response: The requested data were provided and are discussed under Validation above. The response is satisfactory.

e. (b) (4) . Please provide these data for review.

Review of the response: (b) (4) . The results are discussed under Validation. The response is satisfactory.

f. Please provide (b) (4) .

Review of the response: The sponsor determined the (b) (4) An IR was sent to resolve this issue.

The 2nd IRs were sent to the sponsor on March 5, 2018. The responses were received on March 19, 2018 in Amendment 24.

a. Accuracy data in page 36 of the validation report (MVRMQ-BC-0002.03) showed (b) (4) of total protein with (b) (4) of the protein concentration of the prepared samples. Please explain this outcome with supporting data or literature reference.

Review of the response: The sponsor stated that it was noticed during the development study that Damoctocog alfa pegol (b) (4) The response is acceptable.

b. Please provide data to show that (b) (4) in your products not (b) (4) described in the test procedure.

Review of the response: (b) (4) The response is acceptable.

c. (b) (4) indicated on pages 15, 21 and 35 of your method validation report.

Review of the response: The sponsor used the approach of (b) (4) The response is not acceptable.

The 3rd IR was sent to the sponsor on April 5, 2018. The response was received on April 05, 2018 in amendment 34 and on May 14, 2018 in amendment 38.

Regarding the validation reports of method for (b) (4)

(b) (4)

Review of the response: The sponsor initially proposed a (b) (4)

The result is discussed under Validation above. The response is satisfactory.

Conclusion: The analytical procedures of "Quantitation of Moisture (b) (4)

Protein Content (b) (4) " are adequately described and validated for the intended uses.