DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food & Drug Administration
10903 New Hampshire Ave.
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To	STN: #125661/0
From	Parmesh Dutt, DBSQC/OCBQ
Through	Lokesh Bhattacharyya, DBSQC/OCBQ Maryna Eichelberger, Director, DBSQC/OCBQ
Product	Antihemophilic Factor (Recombinant), PEGylated STN: 125661/0, Jivi (BAY 94-9027)
Sponsor	Bayer HealthCare LLC
Subject:	Review Memo for Biological License Application for Antihemophilic Factor (Recombinant), PEGylated, STN# 125661/0, Jivi (BAY 94-9027)
Recommendation:	Approval

Summary of Review

A new BLA was submitted for Antihemophilic Factor (Recombinant), PEGylated, STN: 125661/0 - Jivi (BAY 94-9027) by Bayer HealthCare LLC. This memo applies to the review of the rFVIII potency assay using chromogenic method and its validation, for its use in testing the potency of the (b) (4), drug product (b) (4) Four IRs were submitted on December 6, 2017, March 30, 2018, April 6, 2018, and June 1, 2018; the responses were received on December 15, 2017, April 5, 2018, May 15, 2018 and June 7 respectively. Based on the original submission and additional information provided in response to the IRs, it is concluded that the method is described and validated adequately for its intended use.

Background

The drug product BAY94-9027 (Proprietary name: Jivi) is a recombinant (r) B-domain deleted (BDD) human coagulation Factor VIII (FVIII), which is conjugated with a 60kDa branched polyethylene glycol (PEG) molecule. Jivi is supplied as single use glass vials containing (b) (4) 500, 1000, 2000 and 3000 International Units (IU) of the product. It is reconstituted with 2.5 mL sterile Water for Injection (WFI). The drug product is indicated for use in previously treated adults and adolescents (12 years and older) with hemophilia A (congenital FVIII deficiency) for (i) on-demand treatment and control of bleeding episodes, (ii) perioperative management of bleeding, and (iii) routine prophylaxis to reduce the frequency of bleeding episodes.

Submitted Information Reviewed

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

-125661/0.0-3.2.P.5.2. Analytical Procedures

- Doc. P.5.2.60-02-v2.2 Test Procedure for Potency and Content: Damoctocog alfa pegol Method: Test Procedure for rFVIII Potency Determination

-125661/0.0-3.2.P.5.3. Validation of Analytical Procedures

- Doc. P.5.3.60-02-v2.0 Validation of Potency Assays and Content: Damoctocog alfa pegol Method Potency - Potency
- Doc. R.6.01-02-v02 Method Validation Reports: Damoctocog Alfa Pegol Method for Potency Chromogenic Method (MVR-MV-BF104-0008.03)

-125661/0.0-3.2.S.4.3. Validation of Analytical Procedures

- Doc. S.4.3.86 -02-v 2.1 Method Development for Potency Assays: Damoctocog alfa pegol Method

-125661/0.0-3.2.P.6 Reference Standards or Materials

- Doc. P.6.01-01 Reference Standard: Damoctocog alfa pegol (b) (4)

-125661/0.10-3.2.P.5.3. Validation of Analytical Procedures

- Doc. P.5.3.60 -03, -04 and -05. Validation of Potency Assays and Content: Damoctocog alfa pegol Method Potency
- Doc. R.6.01-03-v03 Method Validation Reports: Damoctocog Alfa Pegol Method for Potency Chromogenic Method (MVR-MV-BF104-0008); Ver. 6, 7 and 9.

Review Narrative

The proposed specifications for potency of the drug product by the chromogenic Assay (reconstitution vol. 2.5mL):

(b) (4)
500 IU minimum (b) (4)
1000 IU minimum (b) (4)
2000 IU minimum (b) (4)
3000 IU minimum (b) (4)

Method

The test method is described in the document entitled, “Damoctocog Alfa Pegol Method: Test Procedure for Potency and Content,” (Doc. P.5.2.60-02).

Potencies of the drug product (DP) Jivi, (b) (4)
are measured by chromogenic assay using (b) (4)

(b) (4)

The assay acceptance criteria include:

- (b) (4)

Method Validation

The method is validated for analysis of (b) (4) DP, (b) (4) . The sponsor assessed the following validation characteristics: accuracy, precision (repeatability and intermediate precision), linearity, specificity, range and robustness of the method.

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

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

(b) (4)

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(b) (4)

(b) (4)

Information Request and Review

Following IR was sent to the sponsor on December 6, 2017. The response was received on December 15, 2017 as Amendment 10. The IR questions and review of the response are discussed below.

1. For the Linearity Studies presented in Validation report, MVR-MV-BF104-0008.3, you presented (b) (4)

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   Review of Response: The sponsor has provided the (b) (4)

(b) (4) The data and the results are satisfactory.

2. For the Linearity Studies presented in Validation report, MVR-MV-BF104-0008.3, you have presented results from (b) (4) of the target concentration levels. But, reading your report, it appears that all samples were (b) (4) IU/mL for the assay. If that is correct, you provided summary results from (b) (data points in the range (b) (4) in all cases. Therefore, your assay range appears to be (b) (4) .

a. Please clarify if our understanding is correct and provide the details of (b) (4) If you do not agree with our understanding of the assay range, please describe your assay range with appropriate results of linearity, accuracy and precision studies.

Review of Response: The sponsor provided details of the (b) (4) . The potency values used for the method validation (accuracy, linearity and precision) have been tested from (b) (4) . This range corresponds to (b) (4) The data presented is adequate.

b. Please provide linearity results using minimally (b) (4) this range. That is, minimally in the range from (b) (4) to (b) (4) . The linearity should be provided by (b) (4) at each concentration level over the range.

Review of Response: The (b) (4) requested by the IR question. The IR question is addressed adequately.

c. Please provide accuracy results at minimally (b) (data points over the same range as the linearity study.

Review of Response: For the accuracy (b) (4) . Therefore, an IR was sent.

Following IR was sent to the sponsor on March 30, 2018. The response was received on April 5, 2018. The IR questions and review of the response are discussed below.

> While reviewing of your accuracy data, we noted that you determined expected and measured potencies using the same method and using the same standard. Thus, you performed the same assay twice, calling one result as expected potency and the other measured potency. These results do not demonstrate accuracy of your method. The accuracy should be demonstrated by either comparing results obtained using two (b) (4) methods or from (b) (4) experiments, in which estimates of (b) (4) concentrations are obtained using an (b) (4) method or are available from an authoritative source (e.g., WHO; International Standard). Please provide data obtained by either of these two approaches, to demonstrate accuracy of your method by April 16, 2018. If you feel that you will not be able to meet this timeline, please propose the timeline when you can provide the requested data by the above-mentioned date.
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> Review of the response No new data has been submitted to address the IR question. The data points to the data submitted earlier which does not use any (b) (4) method and does not include any (b) (4) experiments to demonstrate accuracy of the method. Another IR was sent on April 6, 2018 to ask for the (b) (4) data.

Following IR was sent to the sponsor on April 6, 2018. The response was received on May 15, 2018. The IR questions and review of the response are discussed below.

> We reviewed your response to our IR, dated March 30, 2018, but did not find data we requested in our IR. In our previous IR, we explained why the data you submitted in support of accuracy of your method were (b) (4) and did not demonstrate accuracy of your method. We requested that you demonstrate the accuracy of your method either by using an (b) (4) method or from (b) (4) results obtained by (b) (4) Please provide the data requested by April 20, 2018. If you feel that you will not be able to meet this timeline, please propose the timeline when you can provide the requested data by the above-mentioned date.
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> Review of response
> The sponsor conducted new (b) (4) studies to support the accuracy of the method. Sponsor's provided new data which is reviewed and discussed above under accuracy. The IR has been addressed adequately as has been discussed above.

d. Please provide repeatability results over the above-mentioned range.

> Review of Response: Sponsor has clarified that the linearity and intermediate precision study results provided good estimates of the repeatability of the assay over the range tested because these studies were done in (b) (4) at each data point. The assay was performed at (b) (4), which

covers the testing range of the method (b) (4) ranged from (b) (4). The data meets the acceptance criteria for (b) (4) of not more than (b) (4) over the range. The IR question has been answered adequately.

Following IR was sent to the sponsor on June 1, 2018. The response was received on June 7, 2018. The IR questions and review of the response are discussed below.

1). For the specificity study, you used the (b) (4) the drug product but (b) (4). Therefore, the issue of specificity could be more critical for (b) (4) DP. Please provide the data to demonstrate specificity of the method for (b) (4)

Review of the response
Sponsor indicated that (b) (4) The results support the specificity of the test method. The response addresses the IR adequately.

2). (b) (4) (as per Val Doc No: MVR-MV-BF-104-0008.03 and MVR-MV-BF104-0008.06). However, your acceptance criterion in document S4.3.86-02, Method Development for Potency Assay was (b) (4) in the acceptance criterion based on your study results or other scientific criteria. If our interpretation is true, please revise your validation report and submit for review.

Review of the response: The sponsor pointed out that they had presented the results for (b) (4) was a typographic error. The IR has been addressed adequately.

3). You used a term "Contrast" in your Table for the result of robustness studies (page 62 of MVR-MV-BF104-0008.06, R6.01-03). You provided no description

of this term and its significance. Please provide a description of this term and explain its significance in your data analysis and conclusion.

Review of the response: The sponsor (b) (4) The response to the IR is satisfactory.

Conclusion: The test method for FVIII potency, the validation reports and sponsor's responses for the information requests have been reviewed. The test method meets the standards and qualifications for testing of FVIII potency in drug product Jivi.