



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To: BL STN 125444/0 and Edward Thompson
From: Andrey Sarafanov, PhD, OBRR/DH/LH
Applicant: Biogen Idec, Inc.
Product: Coagulation Factor IX (Recombinant), Fc Fusion Protein
Subject: Chemistry, Manufacturing and Controls Analytical Methods Review
Through: Mark Weinstein, PhD, OBRR/IOD
Basil Golding, MD, Director, DH/OBRR
CC: Tim Lee, Nancy Kirschbaum, Ze Peng, La’Nissa Brown, Carl-Michael Staschen, Stephanie Omokaro, Ellen Huang, Loan Nguyen, Anthony Hawkins, Bethany Baer, Judy Li, Catherine Poole

EXECUTIVE SUMMARY

This memorandum summarizes the review of product-related information in an original Biologics License Application (BLA) under STN 125444 submitted by Biogen Idec, Inc. (Biogen) for Coagulation Factor IX (Recombinant), Fc Fusion Protein (rFIX-Fc). I have reviewed information for validation of the analytical methods used for the drug substance (DS) and drug product (DP) (sections 3.2.S.4.2, 3; 2.S.4.3; 3.2.P.5.2 and 3.2.P.5.3) including information for the reference materials (sections 3.2.S.5 and 3.2.P.6). During review of the submission, information requests (IRs) were sent to the Applicant, who addressed the concerns in a satisfactory way. Based on the totality of this information, I found this BLA to be approvable.

ASSAY METHODOLOGY AND VALIDATION FOR DRUG SUBSTANCE

(3.2.S.4.2 and 3.2.S.4.3)

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b(4)

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7 Pages determined to be not releasable: b(4)

ASSAY METHODOLOGY AND VALIDATION FOR DRUG PRODUCT

(3.2.P.4.2 and 3.2.P.4.3)

Analytical Procedures Used to Test rFIX-Fc Drug Product

Attribute	Test Method	Section Reference
General	Appearance	3.2.P.5.2.1
General	Residual Moisture	3.2.P.5.2.2
General	Appearance of solution after reconstitution	3.2.P.5.2.3
General	Reconstitution Time	3.2.P.5.2.4
Safety	Particulates	3.2.P.5.2.5
General	b(4) of Reconstituted Product	3.2.P.5.2.6
General	b(4)	3.2.P.5.2.7
Identity and Biological Activity (Potency and b(4))	Coagulation Assay (aPTT)	3.2.P.5.2.8
Identity and Purity and Impurities	b(4)	3.2.P.5.2.9
Identity and Purity and Impurities		3.2.P.5.2.10
Purity and Impurities		3.2.P.5.2.11
Purity and Impurities	Activated FIXFc	3.2.P.5.2.12
Quantity	Protein b(4)	3.2.P.5.2.13
Biological Activity	b(4)	3.2.P.5.2.14
Safety	Endotoxin	3.2.P.5.2.15
Safety	Sterility	3.2.P.5.2.16
Safety	Container Closure Integrity	3.2.P.5.2.17

Reference Materials (3.2.P.6)

Reference standard used for testing the rFIX-Fc DP ---b(4)-----

1. APPEARANCE (LYOPHILIZED DRUG PRODUCT)

DP sample is visually inspected for color of the lyophilized cake under -b(4)-----
----- Because the method is compendial, according to ICH Q2(R1) guide, validation was not performed (3.2.P.5.3.1).

2. RESIDUAL MOISTURE

The residual moisture was determined using a ---b(4)-----

The method was assessed (3.2.P.4.3.2) for specificity, linearity, range, accuracy, quantitation limit, precision (repeatability, intermediate precision, and reproducibility) and robustness. The moisture content is expected to be -b(4)----- for all DP formulations. Therefore, the method's performance was assessed up to -b(4)-

(w/w) moisture, which includes the expected range. In this study, the DP strength of –b(4)– , 500, 1000, 2000 and 3000 were used. Specificity was inferred from the recovery of –b(4)–. The (b)(4) and the 3000 IU/vial DP were used for specificity assessment, –b(4)–. The quantification range was determined as –b(4)– (from –b(4)– to 3000 IU/vial strength, respectively). In the study, all acceptance criteria were met, and the method was considered suitable for determination of moisture content of rFIX-Fc lyophilized DP (report C10-029-2136A).

Reviewer's Comment

Considering the criticality of the Residual Moisture for the DP stability, suitability of the method to measure this parameter should have been assessed by testing comparability of this method with another method, which is well-established, such as the –b(4)–. Biogen responded to an informational request, on August 09, 2013, as reviewed under Informational Requests (Question 4). The response was considered insufficient, and an additional request to resolve the issue (Question 6), was sent on September 19, 2013. Biogen committed to perform such a study (Amendment 28, Question 4), and on October 31, 2013 (Amendment 43), provided the results. In this study, the –b(4)–method was demonstrated to be comparable with the –b(4)– method for the analysis of moisture in the DP. Thus, the issue was addressed appropriately.

3. APPEARANCE OF SOLUTION AFTER RECONSTITUTION

An aliquot sample of rFIX-Fc DP after reconstitution is visually inspected for color and clarity according to the method described in the Section –b(4)– Analytical Procedures. –b(4)–. Assessment of visible particles is performed per –b(4)– by observing the sample against the –b(4)–.

Compared to compendial descriptions, the method used has some modifications, such as a –b(4)– during the observation. Biogen states that a full-validation study is not required as the method is compendial [Q2(R1)], and qualified the method versus the compendial method for comparability (3.2.P.4.3.3).

4. RECONSTITUTION TIME

To determine the reconstitution time, the lyophilized rFIX-Fc DP is added by the diluent and gently mixed. The time of dissolution is measured. The suitability of the method for release and stability testing of rFIX-Fc DP was evaluated by the determination of precision (3.2.P.5.3.4). In this study, the DPs of –b(4)– , 1000 and 3000 IU/vial strengths were used. Precision (RSD) was –b(4)– that was considered acceptable, since the reconstitution procedure is a subjective procedure, and the results were within the expectations for such methods (report TR-AT-000041).

5. PARTICULATES

Particulate analysis is performed using –b(4)– in accordance with the current –b(4)–. Since the method is compendial, validation of it was not provided (3.2.P.5.3.5).

Reviewer's Comment

According to –b(4)–, this method is relevant to –b(4)–. Another method to measure particulate matter in injected material is –b(4)–.

6. –b(4)- OF RECONSTITUTED PRODUCT

The method (3.2.5.2.6 and 3.2.P.5.3.6) –b(4)-----

7. –b(4)-----

--b(4)-----

8. COAGULATION ASSAY (aPTT)

--b(4)----- (3.2.P.5.2.8 and 3.2.P.5.3.8), -----
b(4)----- Biogen stated that since the method is compendial,
validation was not required. In the Amendment 12 (Section 3.2.S.4.3.4, Report B10-029-2145A), it is stated
that the assay is qualified for the testing of rFIX-Fc release and stability for reference standard, b(4) DP.

Reviewer's Comment

The comment is similar to that for b(4). Validation of the method is relevant to analyzing rFIX-Fc
reference material only, but not the DP due to the difference in the matrix composition (formulation
buffer) between these entities. Thus, the concern that the method could be not validated for DP also
remained. In response to a request to validate the method for –b(4)- DP, Biogen provided information on
August 09, 2013, which was reviewed under Informational Requests (Question 2). The issue was
addressed appropriately.

9. ---b(4)-----

--b(4)-----

10. –b(4)-----

--b(4)-----

11. –b(4)-- -----

--b(4)-----

12. ACTIVATED FIX-Fc (rFIXa-Fc)

--b(4)-----

13. PROTEIN –b(4)-- -----

--b(4)-----
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Reviewer's Comment

The method is described as the same for –b(4)- DP. At the same, under the b(4) specifications, this method is listed as “Protein –b(4)-----” and, under the DP specifications, is listed as “Protein --b(4)-----”. Upon a request to comment on it, on August 09, 2013, Biogen responded that both methods are the same for –b(4)---- DP (Informational Requests, Question 5). The concern was addressed appropriately.

14. ---b(4)-----

--b(4)-----

15. ENDOTOXIN

--b(4)-- -----
----- Upon FDA request to provide validation data to support determined DP sample --(b)(4)-- and lack of interference of the product matrix, Biogen provided following information. (b)(4) lots at the lowest strength (b(4) IU/vial) and (b)(4) lots at the highest strength (3000 IU/vial) of the DP were tested using endotoxin standard spiked into the samples. Spiked endotoxin standard was recovered at the range of -b(4)--- in the above (b)(4) samples. Based on the test sensitivity, the respective maximal sample (b)(4) (MVD) were determined as –b(4)-- -----
----- These data also indicated lack of the matrix interference. Supporting documentation is provided in Amendment 7 (February 20, 2013).

16. STERILITY

The method is performed using membrane filtration in accordance with the current –b(4)-----
----- Since the method is compendial, validation is not required per ICH guidance Q2(R1).

Reviewer's Comment

Although it would be more relevant if the test microorganisms had been spiked into the reconstituted DP, but not into the –b(4)----- the protocol that was implemented follows the compendia.

17. CONTAINER CLOSURE INTEGRITY

Container closure integrity is conducted in lieu of sterility for stability testing per ICH Q5C using a –b(4)-----
----- method. DP vials and positive controls consisting of breached rFIX-Fc DP vials are placed ---b(4)-----, and upon reconstitution of the DP, the

Question 3 (#36 in the Response). Regarding the test for –b(4)–, please provide further detail on method development for generation of the detecting –b(4)–. Specifically, please provide evidence that the –b(4)– is capable of detecting all –b(4)–

Response. --b(4)-----

--b(4)-----

Question 4 (#37 in the Response). Please provide validation of the –b(4)– test against the accepted, compendial –b(4)–test. Please provide further detail regarding the procedure for –b(4)– the drug product lyophilized cake used in the method.

Response. A comparison of the –b(4)– method to the –b(4)– method was conducted using (b)(4) different DP lots with residual moisture (RM) in the range of –b(4)– and the same amount of –b(4)–. The data presented indicate that moisture content determined by the two methods may be comparable. The description of –b(4)– procedure is provided.

Reviewer Comment. The RM range tested is below the DP RM specification limits (–b(4)–). Some samples tested by –b(4)– method were –b(4)– (or data not available), in contrast to the same samples tested by –b(4)– test, thus the respective data are not quite comparable. In addition, at least two dosages of the DP such as b(4) and 3000 IU/vial (following the –b(4)– strategy) should have been tested instead of samples with the same amount of –b(4)–. The study cannot be considered as validated; thus the response was not acceptable. An additional IR was sent on August 29, 2013 and responded as below.

Question 5 (#38 in the Response). Please clarify whether or not the analytical procedure for protein determination in –b(4)– drug product are the same.

Response. Biogen explained that the analytical procedure for protein –b(4)– determination is the –b(4)–DP.

Reviewer Comment. The response is acceptable.

On August 29, 2013, the following additional IR (question #4) was sent to Biogen.

Question 6 (#4 in the IR). Validation of the ---b(4)----- method against the -b(4)----- method for determination of residual moisture was not adequate in that: (a) the validation study did not cover the full acceptance range of -b(4)---, specified for rFIX-Fc drug product shelf-life and (b) the study did not include -b(4)----- and 3000 IU dosage presentations.

Responses

On September 19, 2013 (Amendment 28), Biogen responded that they were conducting an addendum comparability validation of the ---b(4)----- method against the compendial -b(4)----- method. This addendum would include a linearity study by both methods up to -b(4)----- and both the b(4) IU/vial and 3000 IU/vial dosage presentations. As discussed at the September 12, 2013 late stage meeting, Biogen would complete this study and submit the data to the agency by November 1, 2013.

On October 31, 2013 (Amendment 43), Biogen provided the results of the study, in which both methods, the compendial -b(4)-----) and the -b(4)-----method, were compared (Report TR-AT-005098). The parameters studied were Linearity and relative Accuracy and relative Precision (comparability), and the samples used were DP of b(4) IU/vial and 3000 IU/vial strengths (b(4) lots).

The linearity of the method was determined by comparing the amount of (b)(4) measured to the amount expected over the range (from -b(4)----- and from -b(4)----- for b(4) IU/vial and 3000 IU/vial, respectively) for both methods. The linearity results met the acceptance criteria (-b(4)-----).

The relative accuracy was assessed by comparing the RSD for % moisture by the -b(4)----- method to that of the -----b(4)--- method, which were (b)(4) for the b(4) IU/vial and (b)(4) for the 3000 IU/vial, respectively. The relative precision was assessed by comparison of the mean RSD values (%), which were (b)(4) for the -b(4)----- and (b)(4) for the -b(4)----- for -b(4)- IU/vial sample. All results met the acceptance criteria, and we concluded that the methods are comparable.

Reviewer Comment. The response is acceptable.

REVIEWER'S COMMENTS

All analytical methods used for characterization of identity, purity, quality and safety of rFIX-Fc -b(4)----- Drug Product were adequately validated to support the Specifications.

CONCLUSION

From the analytical methodology perspective, this BLA is approvable.