



## 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)

[  
  
b(4)  
  
]

**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)-



**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)-  
-----  
-----





**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.