

Record of Telephone Conversation, February 28, 2013 - RIXUBIS

Submission Type: BLA Submission ID: 125446/0 Office: OBRR

Product: Coagulation Factor IX (Recombinant)

Applicant: Baxter Healthcare Corporation

Telecon Date/Time: 28 February 2013, 03:00 PM Initiated by FDA? No

Communication

Category: Advice

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Telecon Summary: Provide clarification for the information request sent on February 22, 2013

FDA Participants: Tim Lee, LH/DH/OBRR/CBER

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Telecon Body

Provide clarification to Baxter for the following issues:

1. Justifications for not including ---b(4)----- assays on the specification for BAX326 BDS were previously provided within the impurities, characterization and PV sections of the original BLA. -b(4)----- is routinely monitored as an in-process control parameter. Baxter requests clarification if the BLA justifications for these parameters were deemed insufficient.

2. The Agency's below information request refers to a stability criteria of -b(4)---- however, Baxter recently submitted responses to the Agency's Form 483 in which the stability criteria of -b(4)---- was proposed. Baxter proposes to respond to the below information request with -b(4)-----

3. Baxter is evaluating the timelines to a complete response to the information request and at this time, it appears that responses to a few questions may not be available a couple of weeks after the requested March 10 date. Baxter wishes to communicate to the Agency, the specific responses that may be delayed so that any risk to the BLA review and proposed FDA action date can be assessed by both parties separately.

The following information request (IR) was sent on February 22, 2013:

1. Regarding the multiple out-of-specification (OOS) potency measurements observed in the stability studies, please provide a report with the evaluation of all existing stability data in which OOS potency events are determined against the most current specifications. The report should include assessment of the potential impact of these OOS results on the proposed shelf-life and in-use stability of the Bulk Drug Substance (BDS) and Final Drug Product (FDP).

2. With regard to the poor robustness of the potency assay as a possible root cause for the OOS results during stability evaluations, please
 - a. Explain the discrepancies in the Factor (F) IX potency values determined by the clotting and -b(4)----- assays;

b. Provide a table that compares the assay conditions and known assay deficiencies for all versions of the potency assay as well as the dates when the specific assay versions were introduced, starting from the beginning of process development;

c. Evaluate the impact of the poor assay robustness on the process validation studies, potency assignment of standards, batch analyses and interpretation of clinical studies, including but not be limited to recoveries and other parameters in the PK studies;

d. Retest all product batches used in pre-clinical, clinical, and process validation evaluations, and provide a table that compares the original and retested FIX potencies, as well as the FIX activity by the chromogenic assay.

3. Regarding the BDS and FDP release specifications, please

a. Establish the FDP potency specifications which are applicable to each of the nominal vial strengths, e.g., “within minus n% and plus m% of the nominal vial strength”, where “n” and “m” values are derived from the existing manufacturing experience with the respective nominal vial strengths. In addition, please add the following –b(4)----- requirement to the potency ---b(4)-----

b. Provide justification for the FDP and b(4) specifications on FIX potency and pre-activation (FIXa impurity) using the data from the lots manufactured for pre-clinical, clinical, and process validation evaluations;

c. Add the following parameters to BDS specifications, levels of –b(4)-----

d. Develop appropriate in-process control limits and/or BDS specifications to demonstrate consistent removal of the –b(4)---- impurity in the product.

4. The batch analysis tables indicate that FIXa activity assay experienced variations due to changes of reagents. Please submit completed investigation reports on this deviation.

5. Regarding the Sterility/Bioburden Test:

a. Sterility method validation (3.2.P.5.3) for the suitability of the method for rFIX FDP was performed by the –b(4)----- method. Baxter stated in the document in Section 3.2.P.5.2 Sterility that the sterility method is described in more detail in ‘OR-12-00005-CTP00.04’. However, the test procedure ‘OR-12-00005-CTP00.04’ describes the –b(4)----- method. Please clarify at what processing stage is Sterility/Bioburden tested using the --b(4)----- method.

b. For the Sterility Validation Report ‘Doc ID OR-12-00006-CVRH9.02’ a consolidated report was submitted that has either missing or unreadable lot data on pages 2, 5, 6, 7 of 8, please send the completed validation report to include the method procedures and all data.

6. Regarding the Endotoxin test, please

a. Provide a comparative description of all Endotoxin test methods used for the control of the –b(4)- and FDP manufacture.

b. Provide relevant validation reports for each of the endotoxin test methods showing method suitability for the –b(4)- and FDP.

c. Correct the inconsistent description of the endotoxin test method in the BLA. According to the validation study ‘Doc ID OR1300043-CTP00.03’ endotoxin is performed by the ---b(4)----- method. However, the validation report ‘OR-13-00043-CVRH9.01 includes only the qualification of the –b(4)----- method.

Discussion during Teleconference:

§ Baxter indicated that responses to some questions may require additional time, e.g., retest of all batches (Question 2.d). Baxter requested the extension of the responses to these sections of the above information request from March 10, 2013 to March 29, 2013. Remaining responses will be submitted on March 10, 2013. FDA agreed to the revised response date.

Baxter inquired on the retesting of all product lots to include the expired and –b(4)-- formulation lots. FDA indicated that the data from all lots would be useful but Baxter should indicate which of the retested lots were expired or formulated differently. FDA also explained the importance of being able to establish a linkage between lots used in the various phases of product development. This information is essential in writing a pertinent dosing regimen related to the potency on the label based on the results of the clinical studies.

- Baxter inquired about the impact of submitting the results in late March on the BLA action due date. FDA discussed the issue of the review timeline and potency assay. Although the timing of the submission of the responses to the IR is reasonable, the scope of the issues related to the potency assay remains unknown. Clinical study results, process validation and stability studies can be potentially affected by poor performance of the potency assay. Therefore, the FDA can only determine if the submitted responses would be classified as a major amendment after we review the information including the requested risk analysis reports.
- Baxter proposes to monitor –b(4)----- campaigns. FDA indicated that –b(4)----- should be added to the –b(4)- specifications at this time because the facility and manufacturing process are new and we do not have sufficient manufacturing experience to remove residual levels of the --b(4)----- from the specifications. When sufficient data are obtained, Baxter can submit a Prior Approval Supplement with justifications to request removal of these parameters from the specifications. Data from more than three post-licensure campaigns may be needed.
- Baxter proposes to monitor –b(4)----- campaigns. Baxter cited international regulatory guidance documents that support exclusion of –b(4)----- testing

from the release specifications. FDA requested additional documentation that supports Baxter's position.

- Baxter proposes to monitor –b(4)----- campaigns. FDA indicated that clinical evidence justifies the addition of –b(4)----- as a release specification. Similar to –b(4)-----, Baxter can request removal of these parameters from the b(4) specifications after sufficient manufacturing experience is accumulated post licensure.
- Baxter asks for the acceptability of –b(4)--- stability criteria. FDA indicated that the stability requirement for the potency to be within –b(4)---- of the labeled value throughout product shelf-life is acceptable.