

From: Maruna, Thomas
Sent: Friday, February 12, 2016 1:13 PM
To: 'Janice Castillo'
Subject: Information Request - BLA 125586.0 - Please Respond By February 22. 2016

Importance: High

Attention: Ms. Janice Castillo
February 12, 2016
Sent by email

Dear Ms. Castillo:

We are reviewing your December 17, 2015 biologics license application (BLA) for the following:

STN	Name of Biological Products
125586/0	Coagulation Factor Xa (Recombinant), Inactivated

We have reviewed your submission under modules 3.2.S.4.2 and 3.2.P.5.2 (Analytical Procedures), which you submitted as amendment 1 of STN: 125586 (125586/0.1) and have determined that the following information is necessary to continue our review:

1. For the following assays described in sections:
 - a. Moisture Content (3.2.P.5.2.3)
 - b. Protein Concentration by (b) (4) (3.2.S.4.2.6)

Please confirm if the procedures described in the above mentioned sections of your submission represent final test procedures, as described in your respective SOPs. If they are not, please submit the current, working SOPs.

2. Please submit the current SOPs for the following assays:
 - a. Purity by (b) (4) (3.2.S.4.2.7)
 - b. (b) (4) (3.2.S.4.2.10)
 - c. Direct Potency (3.2.S.4.2.4), TME-0580, (b) (4) : Direct Inhibitor Potency Assay
 - d. Indirect Inhibitor Potency (3.2.S.4.2.5), TME-0583, (b) (4) : Indirect Inhibitor Potency Assay
3. Please provide the information requested below for the test methods, if they were not described in the SOPs requested above.
 - a. (b) (4) assay (3.2.S.4.2.10)
 - i. Is a (b) (4) used with the (b) (4)? If so, please provide information on the (b) (4) used, including supplier and catalog/part number.
 - ii. Please provide the name of the supplier and catalog/part number of the (b) (4) standard used in the (b) (4) assay.

- iii. Please provide the names/descriptions, including compositions, of the preparations used as reference standard and the suitability standard used in the assay. Please clarify if they are in-house standard or commercially available from a US source. If they are available from a US source, please provide the name(s) of the supplier(s) and catalog/part numbers.
- b. Purity by (b) (4) (3.2.S.4.2.7)
 - i. Please provide description of the (b) (4) and (b) (4) (if any), including information regarding its supplier and catalog/part number.
 - ii. Please provide the name/description of the material used as the standard in this assay. Please clarify if it is an in-house standard or commercially available from a US source. If it is commercially available from a US source, please provide the name of the supplier and catalog/part number.
 - iii. Please provide a representative (b) (4) of the drug product, identifying different (b) (4)
 - iv. It is not clear to us what “the reference percent (b) (4)” (in the system suitability section of Table 3.2.S.4.2-5). Please explain.
- c. Direct Potency Assay (3.2.S.4.2.4)
 - i. Please provide the names/descriptions of the materials used as Reference standard and Assay Control in the assay (Table 3.2.S.4.2-2). Are they in-house materials, commercially available from a US source or International Standard (IS) from (b) (4). If they are available from a US source, please provide the name(s) of the supplier(s) and catalog/part numbers. If the standard is an IS, please provide the code number.
 - ii. Are Control Sample and Assay Control mentioned in the section 3.2.S.4.2.4 the same material? If not, please provide the name/description and source of the Control Sample.
 - iii. Please provide the description and source of FXa used in this assay. If it is not an in-house material, please provide the source, including the name of the supplier and catalog/part/code number.
 - iv. Please indicate the incubation temperature for the assay.
 - v. With reference to the System Suitability section of Table 3.2.S.4.2-2, please clarify what is meant by “All valid data points must have a (b) (4) (b) (4) What regression analysis is used to calculate the results (e.g., linear, quadratic, etc.)? What it being described by the term “The calculated ratio of the Assay Window (A-D) values”.
 - vi. Please explain how the potency is determined, specifically how the (b) (4) (b) (4) of the standards, controls and test samples are calculated, and what is meant by the terms (b) (4) and “Target Potency” mentioned in your validity report.
- d. Indirect Potency Assay (3.2.S.4.2.5)
 - i. Please provide the name/description of the material used as Reference standard and Assay Control in the assay (Table 3.2.S.4.2-3). Please clarify if they are in-house materials, commercially available from a US source or

- International Standard (IS) from (b) (4) . If they are available from a US source, please provide the name(s) of the supplier(s) and catalog/part numbers. If the standard is an IS, please provide the code number.
- ii. Please provide the description and source of FXa used in this assay. If it is not an in-house material, please provide the source, including the name of the supplier and catalog/part/code number.
 - iii. Please indicate the incubation temperature for the assay.
 - iv. In the System Suitability section (Table 3.2.S.4.2-3), please clarify what is meant by “All valid data points must have a (b) (4) What regression analysis is used to calculate the results (e.g., linear, quadratic, etc.)? What it being described by the term “The calculated ratio of the Assay Window (D-A) values”.
 - v. Please explain how the potency is determined, specifically how the (b) (4) of the standards, controls and test samples are calculated, and what is meant by the terms (b) (4) and “Target Potency” mentioned in your validation report.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your responses as an amendment to this file by February 22, 2016 referencing the date of this request.

The action due date for these files is August 17, 2016.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH
Lieutenant, U.S. Public Health Service
Senior Regulatory Management Officer
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Blood Research and Review
10903 New Hampshire Ave.
Silver Spring, MD 20993
thomas.maruna@fda.hhs.gov
O: (240) 402-8454
www.usphs.gov



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