

Our Reference: STN 125506

Bio Products Laboratory

Dear Dr. Lamb:

We are reviewing your biologics license application (BLA) for Coagulation Factor X (Human) and have the following information request.

1. With reference to your statement in Section 11 **Description** of the Full Prescribing Information “Each vial of COAGADEX is labeled with the factor X potency in International Units (IU).”, please
  - a. Revise the statement to read “Each vial of COAGADEX is labeled with the actual factor X potency in International Units (IU).”
  - b. Add the word “Range” to the potency identifiers on the carton and container labels, e.g., 250 IU Range, etc., and
  - c. Add the actual factor X potency on the COAGADEX carton label.
2. Regarding the Final Drug Product (FDP) release specifications,
  - a. Please provide the justification for the limit of (b) (4) for the parameter “Stability at (b) (4) and submit the *Standard Operating Procedure* for this test.
  - b. In section 3.2.P.5.2 *Analytical Procedures*, you indicated that batches must show no significant defects during the (b) (4) of stability observations. Please explain the (b) (4) requirement and the criteria for “significant defects”.
  - c. Please explain the out-of-specification (OOS) results in the test for *Factor IX Impurity* for batches (b) (4). Please confirm that these batches were rejected.
3. Regarding the identity and purity tests,
  - a. Please demonstrate the ability of the existing and proposed *Factor X* (b) (4) assays to monitor the (b) (4) impurity in the COAGADEX product.
  - b. We agree with BPL’s proposal to continue to retain (b) (4) as investigative tools for use in the event of a quality failure. However, please

establish an identity and purity reference standard, which is derived from COAGADEX, to be included in this analysis.

4. For the assay for (b) (4)  
[REDACTED]
5. Regarding the Bulk Drug Substance (BDS) and FDP stability studies,
  - a. Please explain the OOS result for the parameter *Specific Activity* for (b) (4) batches (b) (4) and (b) (4) [REDACTED]
  - b. We do not agree with your proposal to use nominal potency to set the specification of FDP in stability studies, i.e., 80-(b) (4) IU/mL. Please add the following requirement to the FDP potency stability specification: “Factor X potency should be within 80-(b) (4) of the actual labeled potency value throughout the product shelf-life under the licensed storage conditions.”
  - c. Please re-evaluate the potency results in all stability studies using the FDP shelf-life specification of 80-(b) (4) of the actual labeled potency value.
6. Regarding the evaluation of COAGADEX immunogenicity,
  - a. Please submit results of method qualification for *Factor X inhibitor screen* and *quantitative Nijmegen-Bethesda* assays and describe the measures employed to maintain the acceptable performance of these assays in the COAGADEX clinical trials
  - b. Please comment (b) (4)  
[REDACTED]
7. With reference to the FDP release specification for the “Bacteria Endotoxin Test”, the limit of “(b) (4)” is not representative of your manufacturing experience. Please revise the limit to better represent the Endotoxin content in historical FDP batches or propose an action limit at which investigations will be conducted to ensure the safety of the FDP. Please also provide the calculations used to justify the specification limit on the basis of the maximum expected dose.

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

Please submit your responses as an amendment to this file by September 10, 2015 referencing the date of this request.

The action due date for this file is October 27, 2015.

Please call me or contact me at [pratibha.rana@fda.hhs.gov](mailto:pratibha.rana@fda.hhs.gov)

Pratibha