



Our STN: BL 125506/0

Bio Products Laboratory

Attention: (b) (4)

Dear (b) (4)

This letter is in regard to your biologics license application (BLA) for Coagulation Factor X (Human) manufactured at your Elstree, UK location, submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in amendment 28 dated January 30, 2014, and amendment 29 dated February 3, 2014. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Chemistry, Manufacturing and Controls (CMC):

1. Outstanding issues identified at the Pre-License Inspection performed on 12 - 25 October 2013 at the BPL facilities in Elstree, UK, and described in Form FDA 483 issued on 25 October 2013 have yet to be resolved. Please submit documentation that demonstrates all outstanding inspectional issues identified during the Pre-License Inspection have been corrected.
2. The data you provided have not demonstrated that the following analytical methods used for the evaluation of potency and safety indicating parameters in the Final Drug Product (FDP) are adequately validated:
 - a. In the determination of *Factor X* potency,
 - i. Please revise SOP QCA/00179 to clearly state the assay validity (acceptance) criteria for the standard.
 - ii. Please describe clearly the details of the testing and calculation of potency in your SOP QCA/00089.

- iii. Please provide data to demonstrate the *specificity* of this assay based on the analysis of representative product samples and matrices.
 - iv. Please provide results to support the *accuracy* of your method using your process (b) (4) and the FDP for which this assay is intended. We suggest you evaluate *accuracy* using a spike-recovery method in which you analyze non-spiked samples at different concentrations and the same samples after spiking with known concentrations (IU/mL) of the standard.
 - v. Please evaluate *linearity* at different dilutions of the product (dilution linearity) and show that the linear regression line of the standard and that of the product are parallel within the proposed assay range to validate that interpolation from the standard regression line is appropriate for the determination of the potency of the product.
 - vi. Please provide data to establish the *range* of the assay based on your results of repeatability, accuracy and linearity studies obtained using representative process intermediate and product samples over the intended range of the assay.
 - vii. Please provide data to demonstrate appropriate *robustness* of the assay method using representative process intermediate and product samples for which this assay is intended. The data should demonstrate the effect of small deliberate changes of critical method parameters, such as reagent concentration, incubation time, etc., as applicable.
- b. In the determination of *Total Protein* by (b) (4)
- i. Please provide data to support the *linearity* of the method using representative FDP samples, and to demonstrate *parallelism* between the linear regression fits for the FDP samples and the standard protein used in the linearity study.
 - ii. Please provide data to establish the *range* of the assay based on your results of repeatability, accuracy and linearity studies obtained using representative product samples over the intended *range* of the assay.
 - iii. Please note that the composition of your Internal Quality Control (IQC) is significantly different from that of the product, e.g., the average protein concentration of IQC is (b) (4) whereas the specification limit for the FACTOR X product is (b) (4). As a result, the IQC sample is not representative of the FDP, and it is not likely that any variation in the method will have similar effect on both FDP and IQC. Therefore, please

provide data to demonstrate the *robustness* of your method in studies performed with representative FDP samples.

- c. In the determination of *Moisture* in Freeze-Dried Products by the (b) (4) (b) (4) Method,
 - i. Please demonstrate method *specificity* using representative product samples.
 - ii. Please provide validation data using representative product samples over the intended *range* of the assay. The following characteristics should be addressed: *specificity*, *accuracy* (spike recovery), *repeatability*, *intermediate precision* (multiple analysts, multiple days), *linearity*, *range*, *limit of quantitation (LOQ)* and *robustness* of the assay. We suggest that you spike your sample with different known amounts of water and then assay both non-spiked and spiked samples to calculate recovery.
- d. In the (b) (4) Method for the Determination of *Factor II activity* ((b) (4) Assay),
 - i. Please provide data to demonstrate the *specificity* of this assay based on the analysis of representative product samples.
 - ii. Please provide results to demonstrate method *accuracy* using FACTOR X product samples. We suggest you evaluate *accuracy* using a spike-recovery method by analyzing non-spiked samples at different concentrations and the same samples after spiking with known concentrations (IU/mL) of the standard in such a way that the total concentrations of Factor II in the samples are between the LOQ of the assay and the proposed specification limit.
 - iii. Please provide data to assess the *LOQ* from analysis of representative samples of your product.
 - iv. Please evaluate *linearity* at different dilution of the product (dilution linearity) and demonstrate that the linear regression line of the standard and that of the Factor II in your product are parallel within the proposed assay range to validate that interpolation from the standard line is appropriate for the determination of Factor II content of the product.
 - v. Please re-evaluate the *range* of the assay based on your results of *repeatability*, *accuracy* and *linearity* obtained using representative product samples.

- vi. Please provide data to demonstrate appropriate *robustness* of the assay method using representative product samples. The data should demonstrate the effect of small deliberate changes of critical method parameters, such as reagent concentration and incubation time, etc.
- e. In the determination of *Factor IX activity* ((b) (4) Assay),
- i. Please submit data to demonstrate the *specificity* of the assay by analyzing representative Factor X product samples to show that the results on Factor IX activities are not affected by the matrix at the concentration at which they are expected to be present in the product.
 - ii. Please evaluate *accuracy* using representative product samples. We suggest you evaluate *accuracy* using a spike-recovery method by analyzing non-spiked samples at different concentrations and the same samples after spiking with known concentrations (IU/mL) of the standard in such a way that the total concentrations of Factor IX in the samples are between the LOQ and the proposed specification limit for the product.
 - iii. Please provide data to determine the *LOQ* from the analysis of representative samples of your product for which the assay is intended.
 - iv. Please provide data, including your linear regression plots, to demonstrate *parallelism* between the linear regression fits for the FDP samples and the standard at different Factor IX concentrations.
 - v. Please re-assess the *range* of the assay based on your results of *repeatability*, *accuracy* and *linearity* obtained using representative product samples.
 - vi. Please provide data to demonstrate appropriate *robustness* of the assay method using representative product samples. The data should demonstrate the effect of small deliberate changes of critical method parameters, such as reagent concentration and incubation time, etc.
 - vii. Please provide the SOPs QCA/00042 and QCA/00073.
- f. In the determination of *Non-Activated Partial Thromboplastin Time* (NAPTT),
- i. Please validate NAPTT as a quantitative method with the actual time in seconds as the reportable result. In addition to *specificity*, please provide data to evaluate other validation characteristics appropriate for a quantitative test for impurity in terms of the reportable result.

- ii. Based on our analysis of the calibration (qualification) data for the control you submitted, we found that the Mean ^{(b) (4)} SD values are (b) (4) [redacted]. Please revise your SOP (QCA/00008) to include (b) (4) [redacted] for the blank as the assay validity criteria.
 - iii. Regarding your response that “the operator will review the control chart and if the control result is not (b) (4) [redacted] the assay would be considered invalid, and the results would not be used”, please revise your SOP to include assay validity criteria.
 - iv. Regarding your statement that two dilutions (b) (4) [redacted]) are necessary to ensure that there is no masking, due to either over dilution or matrix inhibition, please include both dilutions as reportable results and revise your SOP (QCA/00008) accordingly.
 - v. You indicated that (b) (4) [redacted] step is not necessary for the Factor X product. Please revise your SOP (QCA/00008) to include this clarification.
- g. In the determination of *Fibrinogen Clotting Time* (FCT),
- i. Please validate FCT as a quantitative method with the actual time as the reportable result. Please provide data to evaluate other applicable validation characteristics for a quantitative test for impurity in terms of the reportable result.
 - ii. Please revise your SOP QCA/00011/15: The Fibrinogen Clotting Time Test to include appropriate and justifiable assay validity criteria.
- h. In the determination of (b) (4) [redacted]
- i. (b) (4) [redacted]
- [redacted]

iii. (b) (4)

[Redacted text block]

- j. In the determination of *Sucrose* by (b) (4)
 - i. Please provide data, including linear regression plots, to demonstrate *parallelism* between the linear regression fits for the FDP samples and the standard at different concentrations.
 - ii. Please provide data to establish the *range* of the assay based on your results of *linearity*, *precision* and *accuracy* evaluation using representative samples of FDP.

k. In the determination of *Citrate* by (b) (4)

- i. Please evaluate *accuracy*, *repeatability* and *intermediate precision* over the actual assay range of (b) (4)
- ii. The *linearity* of the method was evaluated in the range (b) (4), however the *range* of the method was determined to be (b) (4) based on the *precision* and *accuracy* results, which is different than the range in which *linearity* was studied. Please provide additional data for the *linearity* over the stated *range* of the assay or re-define your assay *range* that is supported by *linearity*, *accuracy* and *precision* results.

l. In the determination of *Sodium* by (b) (4), please provide data to show the *linearity* and *accuracy* of sodium response using FDP and *parallelism* between the standard and sample regression lines to demonstrate assay *linearity*.

m. In the determination of (b) (4)

i. (b) (4)

[Redacted content]

v. (b) (4)

3. Please establish specifications for all source materials per the (b) (4), which should include, but not be limited to:
 - a. Release criteria for plasma pools, including Anti-HIV-1 & -2, HBsAg and Parvovirus B19-DNA.
 - b. FACTOR X inactive ingredients, including sucrose, sodium (b) (4) phosphate.
 - c. Chemicals from the Manufacturing Batch Formula, including Citric acid (b) (4), and (b) (4).
 - d. Sterile water for injection.
 - e. Container closure system, including the glass vial.
4. Please provide additional data to validate the following proposed manufacturing options:
 - a. With reference to FACTOR X Manufacturing Batch Formula (Table 3.2.P.3.2-T1), please provide data to validate the option of (b) (4).
 - b. Regarding the validation of the (b) (4).
 - c. With reference to Section 3.2.P.3.3.1.2.8. Step (b) (4) *Aseptic filling and lyophilization*, please provide justifications for the following statement *“Excursions from these expected conditions would not result in batch failure, subject to compliance of the batch with final product specification after appropriate risk- and impact- assessment.”*
5. Please provide the protocol and qualification reports for the establishment of Factor X potency reference standards used for the release of FACTOR X.
6. Please address the following deficiencies regarding (b) (4) and plasma pools:

- a. During the Pre-Licensure Inspection, you indicated that (b) (4) will not be used for FACTOR X manufacture. Please remove references to the use of (b) (4) from the BLA.
 - b. Please remove references to manufacturing steps and conditions that are not relevant to the manufacture of FACTOR X. For example, (b) (4)
 - c. (b) (4) plasma is considered as the source material for FACTOR X. Please transfer the information currently presented in Section 3.2. *Drug Substance* to Section 3.2.S.2.3 *Control of Materials*.
 - d. Regarding Plasma Container Closure System, you indicated that “Alternative containers when evaluated and approved will be accepted.” Please change this statement to “Alternative containers when evaluated and approved will be accepted and reported to the FDA.”
 - e. Please list all the facilities where plasma donations and plasma pools are tested in Section 3.2.S.2.1 *Manufacturers*.
7. Please address the following deficiencies regarding specifications:
- a. (b) (4) Factor X (b) (4) intermediate prepared at the conclusion of Step (b) (4) (as indicated in the Manufacturing Process Chart) qualifies as the Bulk Drug Substance (BDS). Therefore,
 - i. Please list all manufacturing steps leading to this intermediate in Section 3.2. *Drug Substance*.
 - ii. Please develop BDS specifications, which can be comprised of existing parameters and acceptance limits for the intermediates (b) (4)
 - iii. Please provide Batch Analyses for the BDS.
 - b. Please label FDP vials with the actual (not nominal) Factor X potency, and make the following changes to the FDP specification for “Factor X activity per vial”:
 - i. (b) (4) of nominal potency at release.
 - ii. (b) (4) of labeled potency during the shelf-life of the product.
 - c. With reference to the deviation report 62654 related to the rejection of batch (b) (4) due to low potency caused by (b) (4) of Factor X during (b) (4)

(b) (4)

(b) (4)

. Therefore, please establish Factor X

(b) (4)

as an additional identity and purity test for FDP.

Please establish the specification as “comparable to a reference standard which is derived from FACTOR X”.

- d. Regarding the studies of the clotting and chromogenic assays for Factor X potency,
 - i. For all pharmacokinetics (PK) and *in vitro* spiking studies, please evaluate the ratios of chromogenic to clotting potencies using statistical methods described in Bland JM and Altman DG, *Statistical methods for assessing agreement between two methods of clinical measurement. Lancet* 1986;1: 307-310.
 - ii. For the *in vitro* spiking study presented in Table 3.2.P.2.2.3-T16, please explain the following:
 1. The test values from the parallel line clotting assay are noticeably smaller than those from the calibration curve-based clotting assay.
 2. Factor X potency values at release (labeled potency) derived from the clotting assays are noticeably less than those derived from the chromogenic assay.
 - iii. For the PK studies presented in Section 5.3.3 *Reports of Human PK Studies*, please explain why the chromogenic assay gives slightly higher Factor X potency values than the clotting assay, and comment on the potential implications for the safe and effective use of FACTOR X in clinical practice where the clotting assay is used predominantly in clinical laboratories.
8. You listed the minimum required time of the primary and secondary drying phases and the minimum duration of the heat treatment. Please provide the maximum allowed times for the drying phases and terminal heat treatment, and the studies performed to support these limits.

Labeling:

9. Should additional information relating to the safety and effectiveness of this drug product become available before our receipt of the final printed labeling, revision of that labeling, may be required.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our “Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products,” dated February 2000. This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf> or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER’s SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

We acknowledge receipt of your amendments dated January 30, 2014, and February 3, 2014. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment dated February 3, 2014 in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Pratibha Rana, at (301) 827-6124.

Sincerely yours,

Basil Golding, MD
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research