**M E M O R A N D U M**

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**

**Center for Biologics Evaluation and Research**

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**To:** Files of STN 125426/0 [Responses to CR Letter & Form FDA 483]
Tim Lee, Acting Chief, Laboratory of Hemostasis (LH), DHRR/OBRR

**From:** Chava Kimchi-Sarfaty, Chemist, LH/DHRR/OBRR
Chairperson & CMC Reviewer of STN 125426/0

**Subject**: Deficiencies in CMC information in the BLA for Coagulation Factor IX (Recombinant) [IXFINITY™, formerly IB1001] by Emergent BioSolutions, formerly Cangene

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After reviewing the information Emergent BioSolutions submitted to address the deficiencies identified in the Complete Response (CR) Letter issued on 1 February 2013, and observations cited during the (b) (4) inspection of (b) (4), the contract manufacturer of the drug substance of Coagulation Factor IX (Recombinant), I have found the information to be still deficient to support the approval of the BLA, and thus recommend the issuance of another CR Letter with the deficiencies outlined below:

**Chemistry, Manufacturing and Controls**

1. With regard to the (b) (4) please provide the following:

   a. (b) (4)

   b. Reports on complete characterization of three consecutive lots of rFIX (b) (4) Drug Product (DP) manufactured since June 2014.

   c. (b) (4)

d. Data from the comparison of manufacturing-scale and bench-scale (b) (4) campaigns using the last three (b) (4) lots that were tested in your facility. The data should include, but not be limited to, (b) (4) .

2. In your response to item # 1d in the CR Letter and Information Request (IR) dated 6 June 2014 (STN 125426/0031), you submitted results o (b) (4) on three former process lots (b) (4) and three modified process lots (b) (4) after the implementation of several improvements to the (b) (4) method, such as (b) (4)

b. Additionally, please perform (b) (4) analysis on the same samples using a different laboratory. Please ensure that the samples are handled properly before testing.

3. In your response to CR item # 4, you proposed new limits for (b) (4) . However, you have not completed the validation of the (b) (4) Please provide the data.

4. Regarding process-related impurities, please provide the following:

a. Results validating the removal of (b) (4) ), Chinese Hamster Ovary Host Cell Protein (CHO HCP), (b) (4)

b. In your response to CR item # 12c, you noted that no (b) (4) testing or acceptance limits are in place for (b) (4) However, please add these parameters and their respective acceptance criteria to the DP specifications (section 3.2.P.5.1).

5. In your response to CR items # 12 and # 14, you described changes in data processing procedures, and reported that the potency test analyzer for (b) (4) was changed. Please clarify if the change also applies to DP. In addition, please provide data to compare the potency values determined using the (b) (4)

6. In Tables 67 and 78 in your response to CR items # 12b and # 14b, you provided the acceptance criteria and limits for the in-process control parameters for (b) (4) DP manufacture. However, the response is not complete and should be amended with the following information:

a. Per the Agency recommendation in the CR Letter and in the April 2014 IR, (b) (4) In addition, the Agency also recommended including the activity units by which the final product vials are filled in the manufacturing process narrative. Please include (b) (4) and revise the process narrative accordingly.

b. The proposed acceptance criteria for (b) (4) in the Release and Stability Specifications of the DP are too broad, and not representative of the test results derived from (b) (4) lots. Moreover, the acceptance limit for (b) (4) is not aligned with that for potency (the acceptance limit for potency is (b) (4) of the upper limit, while that for (b) (4) of the upper limit. Please revise the acceptance limits based on your manufacturing experience.

c. In the Release and Stability Specifications of the DP, the proposed acceptance criteria for the (b) (4), are too broad, and not representative of the test results derived from (b) (4) lots. Please revise the acceptance limits based on your manufacturing experience.

d. In your response to the April 2014 IR concerning CR item # 5a, the term "FIX (b) (4) is misleading since the (b) (4) method measures antigen (b) (4) ) only, not (b) (4). Please revise accordingly.

7. (b) (4)

8. In Figure 7 of your response to the April 2014 IR concerning CR item # 5a, you provided the (b) (4) However, the report includes the (b) (4) of only one of the (b) (4) . Please include results from all (b) (4) lots (b) (4) in this figure. In addition, please provide the (b) (4) and (b) (4) results of all (b) (4) .

9. In your April 2014 response to the IR concerning CR item # 5c, you provided the Validation Master Plan Summary Report (VAL-90019-01) which contains the generation numbers of three conformance lots. However, this report does not contain detailed information of the study, which should include, but not be limited to, testing for (b) (4) testing. Please provide all detailed results of the process validation study.

10. In your response to observation # 2 in Form FDA 483, you described the changes you will implement in the governing procedures, *QC-1207, Invalid Assay Handling Procedure* and *GMP-0401, Quality Control Laboratory Investigation Procedure.* Your response is deficient in that you did not describe the implementation of the specific instructions regarding invalidated assay in the specific QC laboratory SOPs, and you did not link the governing procedures to the specific SOPs. In addition, you did not describe the training that accompanies the changes in the governing documents. Please implement the referenced changes and provide the revised documents.

11. In your response to observation # 5 in Form FDA 483, you described the changes you will implement to further evaluate the reagents and kits in the QC laboratory. Your response is partially adequate: Although an assessment of some reagents and kits used in the QC laboratory was performed, no stability tests were performed to establish the expiration dates after the reagent containers are opened or stability during testing. Please explain why the proposed stability testing will include only materials that are kept for longer than (b) (4) at the facility, and the exact storage conditions are not stated. Moreover, please specify the reagents listed as "critical reagent" that will be included in stability testing. Stability testing of a portion of the reagents or kits in the QC laboratory may result in potentially inconsistent laboratory results. Therefore, please improve the design of the stability testing of the QC laboratory reagents.