**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**

---

**To:** Files of STN 125426/0 & Edward Thompson, RPM

**From:** Chava Kimchi-Sarfaty, Chemist, Chair of BLA 125426/0, CMC Reviewer, Laboratory of Hemostasis (LH), DHRR/OBRR

**Through:** Mark Weinstein, Associate Deputy Director, OBRR &
Timothy Lee, Acting Chief, Laboratory of Hemostasis (LH), DHRR/OBRR

**Subject**: Review of CMC information in amendments and response to FDA Form 483 by Emergent BioSolutions – Coagulation Factor IX (Recombinant) [IXINITY™, formerly IB1001]

---

## I. Background and summary

IXINITY™, formerly IB1001 is a recombinant coagulation factor IX (rFIX) product intended for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B.

In the second quarter of 2012, Inspiration, the former sponsor for IND 13551, learned that a higher than expected number of subjects in study IB1001-01 developed antibodies at persistent and growing titers. The antibodies were shown to be against host cell proteins (HCPs) in Chinese Hamster Ovary (CHO) cells (Chinese Hamster Ovary protein, CHOP). CHO are the host cells employed to produce IB1001 drug substance. Because of safety concerns, CBER placed study IB1001-01 on clinical hold and informed Inspiration that the product would not be approved in its current form. A Complete Response (CR) letter was also issued for the companion BLA on 1 February 2013. The major CMC deficiencies cited in the clinical hold and CR letters are related to the CHOP impurities, which elicited the development of antibodies in study subjects. Cangene, which acquired all rights associated with IB1001 and IND 13551, responded to the FDA clinical hold letter dated 5 July 2013. The clinical hold was lifted on 26 July, 2013, based on Cangene's validation of a new (b) (4) development of a new sensitive (b) (4) test for CHOP, which supports the removal of the CHOP impurities from the product; and their improvement in the specificity and sensitivity of the assays for CHOP.

On 6 March, 2014 Emergent BioSolutions informed the Agency that Cangene is now a wholly-owned subsidiary of Emergent BioSolutions (Emergent).

Cangene responded to the CR letter on 28 January, 2014. The response to the CR was incomplete and therefore the Agency sent Information Requests on 7 April 2014 and on 21 April 2014. On (b) (4) , Deborah Trout, Rabia Ballica, Mihaly Ligmond (Team Bio) and this reviewer conducted an inspection of (b) (4) , a contracting company for the Drug Substance (DS) manufacturing of IXINITY™ for Emergent BioSolutions. On (b) (4) we issued an FDA Form 483 to (b) (4) . On 26 June, 2014 Emergent BioSolutions and (b) (4) responded to the FDA Form 483.
This memorandum summarizes the deficiencies found while reviewing the CMC information provided by Cangene and Emergent BioSolutions.

## II. Review

2 pages determined to be not releasable: (b)(4)

- (b) (4)

***CR item to be issued:***

With regard to (b) (4) in the manufacturing of recombinant Coagulation Factor IX (rFIX or F90) from August 2013 to May 2014, FDA has following comments:

a. (b) (4)

(b) (4)

c. Please provide reports that (b) (4) three consecutive lots of rFIX (b) (4) Drug Product (DP) manufactured since June 2014.

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

***CR item to issue***:

In your response to item # 1d in the CR Letter, dated 28 January, 2014 and Information Request (IR) dated 6 June 2014 (STN 125426/0031), you submitted results of (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) (4)

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

(b) (4)

***CR item to issue***:

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 submit the validation data.

***II. d. Process-related impurities***

Cangene performed validation studies to show the removal of (b) (4) Chinese Hamster Ovary Host Cell Protein (CHO HCP), (b) (4) . However, the studies were not complete, or only partial data were provided. For example, spiking results for (b) (4) are not provided.

Cangene responded to CR item # 12c on 28 January, 2014 and noted that no (b) (4) testing or acceptance limits are in place for (b) (4) process related impurities. Therefore, they have not added these testing and acceptance criteria to the Drug Product specifications (section 3.2.P.5.1). Acceptance criteria should be set for these two process-related impurities in the Final Drug Product specifications.

***CR item to issue***:

Regarding process-related impurities, please provide the following:

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

2. Acceptance limits to the DP specifications for (b) (4) because it was stated in your response to CR item # 12c, dated 28 January, 2014, that DS is not tested for (b) (4) and there are no DP specifications in place for (b) (4) (section 3.2.P.5.1).

***II. e. Activity of rFIX - instrumentation***

Prior to June 2010 al (b) (4) DP lots were release tested using the (b) (4) analyzer. For (b) (4) lots tested after June 2010, (b) (4) instrument was used. Results of the new analyzer showed higher activity (in average (b) (4) but the reproducibility of results improved (b) (4) Cangene did not provide the data. Cangene did not specify the instrument that is used to test DP activity.

***Reviewer' comments***:
The potency test analyzer was changed for (b) (4), but it's not clear which analyzer is used for the DP. The data to substantiate the claimed differences in potency using the (b) (4) analyzer as compared to the (b) (4) instrument should be provided.
The responses and reports supporting the other changes are complete and satisfactory.

***CR item to issue***:

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)

***II. f. Activity measurement of rFIX***

Cangene responded to CR item 5a and provided information regarding (b) (4) lots that were manufactured during the Former Process. Since Cangene implemented the main change in the Modified Process (b) (4) it is acceptable to review information obtained from these lot. However, Cangene provided the (b) (4) and not in (b) (4) It is acceptable to use (b) (4) and the manufacturing process narrative should also include the

basis by which final product vials are filled by activity units. In addition, for the justification and validation of the (b) (4) Emergent BioSolutions should provide the raw data of the (b) (4)

***CR items to issue***:

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 (b) (4) lots. Please include results from all (b) (4) lots (b) (4) in this figure. In addition, please provide the (b) (4) results of all (b) (4) .

In Tables 67 and 78 in your response to CR items # 12b and # 14b, dated 28 January, 2014, 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:

1. 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.

2. 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.

3. 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.

4. 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 (b) (4) only, not (b) (4). Please revise accordingly.

(b) (4)

(b) (4)

.

***II. h. Validation Master Plan Summary Report***

(b) (4)

***CR items to issue***:

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) . Please provide the detailed results of the process validation study.

***II. i. Quality Control laboratory - results assay reports***

On (b) (4) FDA issued an FDA Form 483 to (b) (4) . On 26 June, 2014 Emergent BioSolutions and (b) (4) responded to the FDA Form 483.

The SOPs used in the QC laboratory do not contain criteria to issue "in valid" vs. out of specification result or open an investigation. As a result, test results from the (b) (4) were invalidated without adequate investigation (for example, test results from the (b) (4)

***FDA FORM 483 OBSERVATION ITEM 2:***
**Results obtained in the QC laboratories were invalidated without adequate investigation. For example, Assay 12A013, file 414A0161- the assay acceptance criteria were not met and the assay was categorized as invalid.**

(b) (4) ***response to FDA FORM 483 OBSERVATION ITEM 2:***
(b) (4) describes the changes they will implement in their governing procedures, QC-1207, Invalid Assay Handling Procedure and GMP-0401, Quality Control Laboratory Investigation Procedure. This step will be completed by 31 July, 2014. In addition, (b) (4) committed to track the invalid assay metrics and trend it. This step will be completed by 31 August, 2014.

***Reviewer's comments:***

CMC response is partially adequate (b) (4) did not mention the implementation of specific instructions regarding invalidated assay in the specific SOPs of the assays run at their laboratories or the training that will accompany the changes in the governing documents.

***CR item to issue***:

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 invalid assay handling 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.

***II. j. Quality Control laboratory - stability studies***

On (b) (4) FDA issued an FDA Form 483 to (b) (4) . On 26 June, 2014 Emergent BioSolutions and (b) (4) responded to the FDA Form 483.

There are no set time limits for reagents and kits or stability studies that are used in the laboratory, specifically time limits allowed to keep these reagents at room temperature and the number of times a reagent or kit is shifted from (b) (4) The QC laboratories are using the kits or reagents per the vendor expiration date. Although in most cases the kits or reagents are consumed faster than the expiration, the kits and reagents might be compromised because they are kept for too long at the bench. Occasionally a technician repeats a test and therefore keeps the reagent(s) or the complete kit for longer time at the bench. In addition, a sample may be used for additional re-test if the test is concluded as "invalid" and then kept for several hours at room temperature with no validation to show that the sample was not compromised.

***FDA FORM 483 OBSERVATION ITEM 5:***
**No stability studies were conducted on reagents in the QC laboratories.**

(b) (4) ***response to FDA FORM 483 OBSERVATION ITEM 5:***
(b) (4) noted that an assessment of the reagents that are used in the QC laboratory was performed. However, "*QC-1246, Qualification and Validation of Analytical Procedures,* will be revised to require that, as part of method validation, stability criteria are established for all critical QC test reagents for validated methods if held for a period o (b) (4) ." In addition, (b) (4) have committed to confirm "critical reagent stability for all validated Factor IX test method reagents. The studies will include, as appropriate, expiration dates after opening, bench stability during testing, and overall stability requirements."

***Reviewer's comments*:**
CMC response is partially adequate. Although the assessment of the QC laboratory was performed, no stability tests were executed such as expiration dates after opening, or bench stability during testing. It is not clear why their stability testing will include materials that are kept for longer than (b) (4) at the

facility and the exact storage conditions are not listed. Moreover it is not clear which reagents are listed as a "critical reagent."

***CR item to issue***:

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 to be 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.

## III. Summary and recommendations

Emergent BioSolutions did not respond adequately to the FDA 483 items. In addition, some of the information provided by Emergent BioSolutions is inadequate. Therefore, a Complete Response letter with the items specified above should be issued.