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

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Through: Mark Weinstein, Associate Deputy Director, OBRR &
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Subject: Review of CMC information in amendment 35 (Sequence 0036; response to the Information Request sent on June 20. 2014) by Emergent for 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 (DS). 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.

Cangene responded to the first clinical hold on 5 July, 2013, and responded to the CR letter on 28 January, 2014. This memorandum summarizes the review of the CMC information provided in amendment 35, with specific regard to the CR of 1 February 2013, items 10-16.

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

Emergent's incomplete response to the FDA Form 483 regarding the observations cited during the (b) (4) inspection of (b) (4) , their incomplete response to Information Requests sent on 7 April 2014 and on 21 April 2014, and additional deficiencies noted by other disciplines led to the issuance of a Complete Response Letter on 29 July 2014.

The Information Requests listed below should be conveyed to Emergent BioSolutions. Emergent BioSolutions is expected to respond by November 15, 2014.

II. Review

FDA IR #1 of June 20. 2014: 1 February 2013 Complete Review item 10c
You provided a new table labeled as Table 44 in the response (Sequence 0019) to clarify the values of Table 3 presented in section 3.2.S.2.5. You have stated that a corrected version of section 3.2.S.2.5 was also provided. However, the new Table 44 now consists of new values and much of the data presented earlier is omitted. Please submit the corrected table corresponding to Table 13 in BLA Sequence 0004 and highlight/clarify the changes you have made to the original Table which resulted in the new data currently in Table 44.

Emergent's response:
Emergent provided an amended table titled (b) (4) Process Validation Acceptance Criteria and Results" which contains the correct validation data for (b) (4) . Emergent indicated that replacing this table with Table 12 in section 3.2.S.2.5 *Process Validation and/or Evaluation* is not suitable due to a different risk approach and the most recent conformance campaign data is provided in Table 12, section 3.2.S.2.5 in the current CTD component of the application.

Reviewers' comment:
This information is acceptable.

FDA IR #2 of June 20. 2014: 1 February 2013 Complete Review item 10d
You have provided validation study data demonstrating that the conditions and performance parameters of the small-scale runs are fully representative of the commercial scale process for the (b) (4) . However, the following deficiencies should be addressed and completed in order for the reviewers to finalize the review on this topic:
Please incorporate Tables 45-48 in the response of January 27, 2014, into the current section 3.2.S.2.5.
Please provide a detailed comparison of the lab-scale to the full-scale process, specifically illustrating the differences between lab and the full-scale (b) (4) for each (b) (4) step.
The information and data on (b) (4) studies, shown in section 3.2.S.2.5.4.3 (b) (4) Performance over Time in the amendment 4 of the BLA (Table 21-24) has been deleted in the current version of section 3.2.S.2.5. Please include this information and data.

Emergent's response:
Emergent incorporated the data that was presented in Tables 45-48 of the amendment sequence 0019 into Tables 26-29, section 3.2.S.2.5 *Process Validation and/or Evaluation.* Section 3.2.S.2.5.4.3 (b) (4) *Performance over Time* was placed back to 3.2.S.2.5. Also a detailed table of the differences between lab-scale and manufacturing-scale (b) (4) was provided.

Reviewers' comment:
This information is acceptable.

FDA IR #3 of June 20. 2014: 1 February 2013 Complete Review item 10d and 10e
You have provided partial data supporting the validation of (b) (4) However, you have not completed the validation of (b) (4) . In addition, you have not completed the validation of (b) (4)
Please provide the required data.

Emergent's response:
Emergent provided the validation study and acceptance criteria supporting the (b) (4) parameters for the (b) (4) and incorporated the information into section 3.2.S.2.5.4.5 (b) (4) *Studies* as Table 41

and Table 42. A time limit of (b) (4) has been established for the (b) (4) , based on review and assessment of (b) (4) historical manufacturing-scale data including two IB1001 process validation conformance campaigns. Manufacturing batches captured in this data set met all quality attributes and release specifications. This limit will be incorporated into the next (b) (4) run. This limit and its validation were not included in section 3.2.S.2.5 of current CTD component.

Reviewers' comment:
The information is not complete. Emergent should amend the CTD component of the application with the validation study and the new limits.

FDA IR #4 of June 20. 2014: 1 February 2013 Complete Review item 11
You have provided results from clearance studies for the following process related impurities (b) (4) CHO HCP, (b) (4) . However, you have not provided the spiking test results for the process-related impurities (including Chinese Hamster Ovary Host Cell Protein (CHO HCP)) at the laboratory-scale. Please provide the required data.

Emergent's response:
A spiking study for CHO HCP has not yet been executed and is planned for the (b) (4) step; Emergent committed to provide the information prior to September 30, 2014, but it was not yet submitted.

Evaluation of HCP is currently performed for (b) (4)

Material outside of this specification would not be released for use.

Reviewers' comments:
The information is incomplete. Emergent committed to provide the spiking test results for the Chinese Hamster Ovary Host Cell Protein (CHO HCP) at the laboratory-scale and has not yet provided the data.

FDA IR #5 of June 20. 2014: 1 February 2013 Complete Review item 12 and 14
In your response to CR items #12 and 14 you described the changes in the data processing procedures. You have reported that the potency test analyzer was changed for the (b) (4) but you have not clarified how the Drug Product is tested. Please provide this information. In addition, data to demonstrate the differences in potency using the (b) (4) should be provided to ensure consistency in product testing.
The description and reports supporting the other changes are complete and satisfactory.

Emergent's response:
Emergent describes the preparations of (b) (4) DP samples before testing their activity: (b) (4)

The lyophilized DP i (b) (4)

is the contracting company performing all the activity assays
Emergent provided a Report tagged as 20101026-2 comparing the results of (b) (4) potency measurements

using the (b) (4) and (b) (4) measurements using the (b) (4) that was recently introduced by (b) (4) Based on the report Emergent concluded that (b) (4)

Emergent concludes that the potencies measured by these (b) (4) are considered to be equivalent.

(b) (4)

Reviewers' comment:
This information regarding sample preparation is acceptable. (b) (4)

FDA IR #6 of June 20. 2014: 1 February 2013 Complete Review item 12 and 14
In your response to CR items #12 and #14, you have provided the acceptance criteria and limits for the (b) (4) Drug Product:

a. The proposed acceptance criteria for (b) (4) of the Drug Product Release and Stability are too broad and are not representative of the release testing results derived from (b) (4) released lots. Moreover, the limits for the (b) (4) are not aligned with the limits for potency (the acceptance limits for the potency range is (b) (4) the upper limit, while the acceptance limits for (b) (4) are wider (b) (4) of the upper limits. Please set a reasonably narrower range of acceptance limits for (b) (4) .

b. The proposed acceptance criteria for Drug Product Release and Stability Specifications of the upper limits for the (b) (4) are too broad and are not fully representative of the release testing results derived from the (b) (4) released lots. Based on historical data we recommend that it be lowered to (b) (4) Accordingly, please change the acceptance criteria for Drug Product Release and Stability Specifications of the upper limits for the (b) (4) .

Emergent's response:
a. Emergent proposes to adjust the DP (b) (4) specifications for the three DP dosage forms as outlined in Table 1 (copied from Table 7 in the *Response to FDA Information Request Dated June 20, 2014.*). The specifications in section 3.2.P.5.1 are amended accordingly.

Table 1. Proposed DP (b) (4) specification

Vial Dosage (IU/Vial)	(b) (4)
500 IU/vial	
1000 IU/vial	
1500 IU/vial	

b. Emergent proposes to adjust the upper limits of the DP release specification for the (b) (4) This change has not been reflected in the specifications described in section 3.2.P.5.1.

Emergent still proposes to maintain the specification of (b) (4) at the end of shelf life as previously indicated.

Reviewers' comment:
The acceptance criteria for DP release and stability specifications for (b) (4) were only partially amended (line one in Table 1) and therefore Emergent should amend the two other vial dosage specifications (line 2 and 3 of Table 1).

Emergent stated that the acceptance limits of the potency range is (b) (4) of the upper limit, but the actual limits shown in section 3.2.P.5.1 *Specifications* for the 1000 and the 1500 IU vials are not within that range. These should be changed as well.

Figure 14 (*Control Chart for* (b) (4) *Results* (section 3.2.P.5.6, *Justification of Specifications))* and Figure 16 (*Control Chart for* (b) (4) appear identical. Emergent should verify that they represent the (b) (4) as indicated in the title of each figure.

The upper limits for DP release specification for the (b) (4) are amended and now are acceptable. However, this change has not been reflected in the specifications (section *3.2.P.5.1* in the current CTD component) and this section should be amended with the correct values. Emergent did not change the (b) (4) specification for the end of shelf life testing and it remains as (b) (4) without adequate rationale. Emergent should change this specification.

FDA IR #7 of June 20. 2014: 1 February 2013 Complete Review item 12c
In your response to CR item # 12c you have noted that no testing or acceptance limits are in place for (b) (4) process related impurities in the (b) (4). However, you 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.

Emergent's response:
The DP release specification for (b) (4) is set to (b) (4). This is based on the worst case estimation from the results of the testing performed at the (b) (4) stage because (b) (4)
The proposed specification was justified by comparison of the calculated maximum daily exposure and the "No Observed Adverse Effect Level" (NOAEL) reported in rats for oral dosing. The (b) (4) concentration obtained for the (b) (4) will be reported for the final DP.

Emergent set the (b) (4) DP release specification to (b) (4) This is based on the lower limit of quantitation (LLOQ) of the assay used in the testing performed on the (b) (4) rather than at the DP stage, because (b) (4) during the DP manufacturing process. The proposed specification was justified by comparison of the calculated maximum daily exposure and the NOAEL reported in rabbits for intravenous dosing.

Reviewers' comments:
The newly proposed DP release specifications for (b) (4) are acceptable. These specifications are also in the same range of those for other (b) (4) products for intravenous use.

Please note that in both cases, the concentrations measured (b) (4) are used for the DP specifications, although Emergent has noted in their previous response that no testing or acceptance limits are in place to the (b) (4) as process related impurities.

III. Summary and recommendations

The following Information Requests should be conveyed to Emergent BioSolutions. A response is expected by November 15, 2014:

You have provided the acceptance criteria and limits for the (b) (4) Drug Product as a response to February 1st, 2013 Complete Review items 12 and 14:

a. You propose to maintain the end of shelf life specification of the (b) (4) without an adequate rationale. Please amend this value to adhere to the release specifications or provide a rationale for not adjusting this value.

b. The acceptance limit for the potency ranges in section 3.2.P.5.1 *Specifications* were changed for the lower dosage but not for the two other dosages and are not within (b) (4) of the upper limit. Please re-evaluate and amend the acceptance criteria for DP potency release and stability specifications.

c. It is not clear if Figures 14 and 16 coincidently carry the exact same graph although they are labeled to describe the (b) (4) results look identical in the two figures in section 3.2.P.5.6 *Justification of Specifications,* Figure 14. *Control Chart for* (b) (4) *Results* and Figure 16. *Control Chart for* (b) (4)

d. The amended upper limits for DP release specification for the (b) (4) are not reflected in the specification (section 3.2.P.5.1). This section should contain the updated information. Please amend this section in the CTD component of the application accordingly.

e. You have provided results from clearance studies for the following process related impurities: (b) (4) CHO HCP, (b) (4) . However, you have not provided the spiking test results for the process-related impurities (including Chinese Hamster Ovary Host Cell Protein (CHO HCP)) at the laboratory-scale. Please provide the required data.

f. A time limit of (b) (4) has been established for the (b) (4) based on review and assessment of (b) (4) historical manufacturing-scale data including two IB1001 process validation conformance campaigns. Please amend the CTD component of the application accordingly.

g. (b) (4) report # 20101026-2 compares two instruments that are used to determine the rFIX potency. Table 1 illustrates the potency as (b) (4) and does not provide the potency units as in the specifications. Please amend the data to adhere to the same units as in the release specifications of the (b) (4) Drug Product.