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, Iliana Valencia, Chief, Regulatory Project Management Staff & Leigh Pracht, RPM

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

Subject: Review of CMC information in amendment 18 (Sequence 0019; responses 10-16 to the CR letter) by Cangene – 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

Cangene responded to the 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 18, with specific regard to CR items 10-16.

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

The Information Requests listed below should be conveyed to Emergent BioSolutions. Emergent BioSolutions is expected to respond by July 3, 2014.

II. Review

Complete Review item 10:
With regard to process validation (PV) for the Downstream Process Unit Operations, please provide the following:

(b) (4)
(b) (4)

e. Summary of the results from the (b) (4) Time studies.

Cangene response to CR items 10a and 10b:
(b) (4)

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Reviewers' comment:
Cangene committed in their response (dated April 30, 2014, Sequence 0025) to an IR from April 21, 2014 to (b) (4) .

Cangene response to CR item 10c:
Cangene provided data in Table 44 (b) (4) which contains (b) (4) that were unclear earlier in Table 13 of the Amendment 4 of the BLA. Cangene also states that Table 13 in section *3.2.S.2.5* has been corrected.

Reviewers' comments:

The response is not complete, but it satisfies the Agency's request to clarify the incorrect information in Table 3 of section 3.2.S.2.5 in Sequence 0004. The revised section 3.2.S.2.5 *Downstream Process Unit Operations* does not contain a Table corresponding to Table 13 *MBR-1453* (b) (4) *Process Validation Acceptance Criteria and Results* in the BLA Sequence 0004. Table 12 in section 3.2.S.2.5 *MBR-1453*(b) (4) *Validation Result;* (b) (4) *PPQ* is the corresponding Table to this in the most recent version of the application, but the data, the number of runs, and some of the results have been changed without an explanation. Moreover, the values described in Table 44 of the response are not found in Table 12 of section 3.2.S.2.5.

Cangene response to CR item 10d:
Cangene provided summary Tables (Tables 45-48) of the processing conditions and performance parameters for small-scale and full-scale (b) (4) validation studies for each of the(b) (4) process stages. Throughout the small scale studies, the(b) (4) The data of this study are not included in the revised section *3.2.S.2.5*.

All the information and data on(b) (4) studies, shown in section *3.2.S.2.5.4.3* (b) (4) *Performance over Time* in BLA Sequence 0004 (Table 21-24) has been deleted in the current version of section 3.2.S.2.5.

Reviewers' comments:
Cangene 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) (b) (4) .
Cangene states in the updated section *3.2.S.2.5* that small-scale (b) (4)

All information and data concerning (b) (4) studies, shown in section *3.2.S.2.5.4.3* (b) (4) *Performance over Time* in BLA amendment 4 (Tables 21-24) has been deleted from the current version of section *3.2.S.2.5* and this information/data should be returned.

Cangene response to CR item 10d and 10e:
(b) (4) studies have been partially performed at commercial manufacturing scale and are described in section 3.2.S.2.5.
(b) (4)
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Reviewers' comments:
The response is incomplete. Emergent BioSolutions should provide a complete validation of (b) (4) studies of all in-process steps. Moreover, (b) (4)
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Complete Review item 11:

Please provide, in tabular form, results of the clearance studies for the following process related impurities: (b) (4) , CHO HCP, (b) (4) . The tables should include but not be limited to: (b) (4) for each of the referenced impurities.

Cangene response to CR 11:

(b) (4)

Chinese Hamster Ovary Host Cell Protein (CHO HCP) clearance data from (b) (4) manufacturing scale runs, (b) (4) , are provided in Table 62 and Table 63 for (b) (4) steps. Table 64 shows the clearance data for the (b) (4) step that was recently introduced into the commercial manufacturing process for removal of HCP. Total log reduction for CHO HCP is (b) (4).

Reviewers' comment:
The response is not complete. Emergent BioSolutions should provide the spiking test results for the Chinese Hamster Ovary Host Cell Protein (CHO HCP) at the laboratory-scale.

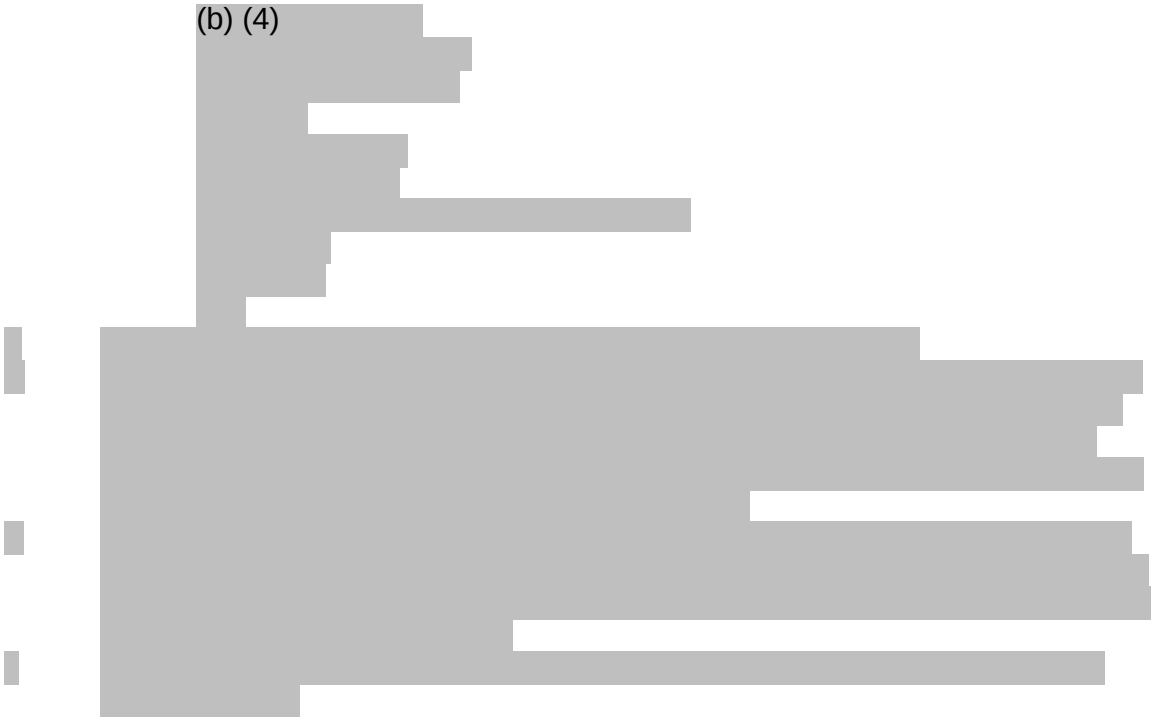
Cangene changed the data processing procedures for the test methods of (b) (4) Drug Product (DP). Therefore, Cangene's response and our review to items 12 and 14 have been combined.

Complete Response item 12:
With regard to Control of (b) (4) Justification of Specifications:

a. Please provide more specific information (e.g., side-by-side comparison between the original and modified results) about the re-evaluation of the original raw specification data using "the current data processing method."
b. Please note that the proposed acceptance criteria for (b) (4) Release and Stability Specification are too broad and not fully representative of the release testing results of the (b) (4) batches. Specifically, please set the acceptance limits based on historical data for the following specification tests:

(b) (4)

(b) (4)



Complete Response item 14:

With regard to Control of Drug Product - Justification of Specifications:

a. Please provide more specific information (e.g., side-by-side comparison between the original and modified results) about the re-evaluation of the original raw specification data using "the current data processing method."

b. Please note that the proposed acceptance criteria for Drug Product Release and Stability Specifications are too broad and not fully representative of the release testing results derived from the (b) (4) released lots. Specifically, please set the acceptance limits based on historical data for the following specification tests:

- Factor IX Potency – the lower acceptance limit should not exceed (b) (4) and the upper acceptance limit should not exceed (b) (4) of the nominal lot potency

(b) (4)

Cangene response to CR 12a and 14a:

Cangene discussed the changes in the following data processing procedures:

- (b) (4)

- Potency: Prior to June 2010 al (b) (4) /DP lots were release tested using the (b) (4) . 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) lower variability). Cangene did not provide the data. Cangene did not specify the instrument that is used to test DP activity.

(b) (4)

Reviewers' comment:
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) instrument should be provided.
The responses and reports supporting the other changes are complete and satisfactory.

Cangene response to CR 12b, 12c, and 14b:
Details of the proposed specifications and justifications can be found in sections 3.2.S.4.1, 3.2.S.4.5, 3.2.P.5.1 and 3.2.P.5.6.
Cangene provided the acceptance limits proposed for the (b) (4) DP release tests. These acceptance limits are proposed based on the analytical data (release and stability) of lots manufactured at (b) (4) released to date, during clinical and nonclinical development, and based on commercial manufacturing process capabilities. This review also encompasses lots manufactured with the modified commercial process. Some of the proposed acceptance limits for DP that have been modified are summarized as the follows:

- Factor IX Potency – The proposed specifications for Factor IX potency have been revised to (b) (4) of nominal potency and are consistent with (b) (4) All the drug product lots have met the proposed acceptance criterion at release and on long term stability.

(b) (4)

- (b) (4)

Cangene notified the Agency that the product lots manufactured by (b) (4) were not used in studying the process capability or stability analysis (for specification setting) as they were manufactured at a (b) (4) and evaluated against different release specifications. (b) (4) lots were used for the clinical testing until 2011.

Reviewers' comments:

(b) (4)

Cangene Response to CR items 12c:

No testing and acceptance limits for (b) (4) process related impurities are in place for (b) (4) DP (based on section *3.2.P.5.1 Specifications*) (b) (4)

Reviewers' comments:

(b) (4)

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Cangene Response to CR items 12d, 12e, 14c and 14d:

Cangene provided in Appendixes 3 and 5 the response to the CR letter CMC items 12d and 14c. Cangene also provided Appendixes 4 and 6, respectively to response to the CR letter CMC items 12e and 14d. Appendix 3 contains a detailed description of FIX (b) (4)

(b) (4)

Reviewers' comment:
This information is acceptable.

Cangene Response to CR items 14e:
(b) (4)

Reviewers' comments:
This information is acceptable.

Cangene Response to CR items 12f and the reviewers' comments were discussed in another review memo dedicated to (b) (4) .

Complete Response item 13:
Please note that your risk assessment of Extractables and Leachables (E&L) for all direct product contact materials and equipment used in the production IB1001 DS is not adequate because it was based solely on the information provided by the vendors. Therefore, please provide results of E&L studies that are specific to the DS manufacturing process and your product. In addition, based on the identified E&L profile, please evaluate the toxicity and potential impact on product quality, including its stability.

Cangene Response to CR items 13:
This section was reviewed by the Pharm/Tox reviewer, Dr. Anne Pilaro.

Complete Response item 15:
Please note that the amount of factor IX activity on the product label of each lot should be the actual activity of factor IX measured at lot release.

Cangene Response to CR item 15:
Cangene agrees with the Agency's comment and will ensure that the amount of rFIX activity on the product label of each lot will be the actual activity of rFIX measured at lot release. Please refer to Section 1.14.1 for example carton and container labels.

Reviewers' comment:
This information is complete.

Complete Response item 16:
With regard to the validation of analytical procedure for Factor IX Potency, please provide the validation study protocol and study report that contains the raw experimental data. In addition, please provide the technical transfer data from the (b) (4), and relevant Standard Operation Procedures for the methods performed at both facilities.

Cangene Response to CR item 16:
To date, all potency testing supporting IXINITY licensure has been performed at (b) (4) Although tech transfers to (b) (4) were performed in preparation for commercial release testing, Cangene has decided that (b) (4) will continue to be responsible for all the release and stability testing; therefore, the tech transfer data supporting (b) (4) is no longer relevant to the program and has not been provided. Cangene provided the validation protocol, validation results including the raw data, and validation study report for the two validation studies:

- Validation study from 2010: covering full validation parameters for (b) (4) and for the (b) (4) DP
- Validation study from 2011: covering additional determination of relative accuracy/precision (b) (4) stability by including additional lots of DP (b) (4) that were manufactured with potency targets of 500, 1000 and 1500 IU/vial instead of (b) (4)

The Standard Operating Procedure (SOP) for the potency assay as performed at (b) (4) is also provided (WI-0351).
The validation study performed in 2011 covered the accuracy and precision (repeatability and intermediate precision) of assays (b) (4) of the samples. The validation study was designed to examine the results produced by (b) (4)

Reviewers' comment:
This information is acceptable.

III. Summary and recommendations

The following Information Request should be conveyed to Emergent BioSolutions. A response is expected by July 3rd, 2014:

1. 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 000 4 and highlight/clarify the changes you have made to the original Table which resulted in the new data currently in Table 44.

2. 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 useful life 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.

3. 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.

4. You have provided clearance studies results for the following process related impurities (b) (4) 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.

5. 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) instrument should be provided to ensure consistency in product testing.
   The description and reports supporting the other changes are complete and satisfactory.

6. 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) of 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)

7. In your response to CR item # 12c you have noted that no testing or acceptance limits are in place to the (b) (4) process related impurities. 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.