**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 & Edward Thompson, RPM

**From:** Chava Kimchi-Sarfaty, Research Chemist, Chair of BLA 125426/0, CMC Reviewer, Laboratory of Hemostasis (LH), DHRR/OBRR & Nobuko Katagiri, Research Biologist, 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 amendment 43 (Sequence 0044; response to the Information Request sent on 10 December 2014) by Cangene Corporation for Coagulation Factor IX (Recombinant) [IXINITY™, formerly IB1001]

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## I. Background and summary

IXINITY™, formerly IB1001, is a recombinant coagulation factor IX (rFIX) product intended for the 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 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 Corporation (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.

On 6 March, 2014 Emergent BioSolutions informed the Agency that Cangene is now a wholly-owned subsidiary of Emergent BioSolutions. The Agency uses Cangene as the Sponsor's name in regard to this submission.

Cangene'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 (IRs) sent on 7 April, 2014 and on 21 April, 2014, and additional deficiencies noted by other disciplines led to the issuance of a CR Letter on 29 July 2014. Cangene responded to this CR letter on 28 October, 2014.

The IRs to the 1 February, 2013 Complete Review items 10, 11, 12 and 14 were sent to Cangene on 4 November, 2014, and Cangene sent its response on 18 November, 2014.

The IRs to the 28 October, 2014 Complete Review items 1-6 were sent to Cangene on 10 December, 2014, and Cangene sent its response on 22 December, 2014. This memorandum summarizes the review of the CMC information provided in amendment 43, with specific regard to the CR of 29 July, 2014 items 1 and 4.

The Information Requests (IRs) listed below should be conveyed to Cangene. Cangene is expected to respond by 26 February, 2015.

## II. Review

*FDA IR #1 of 10 December 2014: 29 July 2014 FDA CR item 1*
With regard to your response to Item #1 of the CR letter:

a. In your response to CR Item #1 you have used a value which you termed equivalence acceptance criteria (EAC). Please explain the rationale to determine the exact value and provide validation.
b. In your response to CR Item #1 you have provided selective raw data for some, but not all lots. Specifically, no raw data were provided for the lots that (b) (4) Please provide all of the data.
c. Please clarify whether (b) (4) was filled into DP because in your response to CR item #1 no DP lots are listed in conjunction with this DS lot.
d. In your response to CR item 1d you have provided bench scale results for rFIX lots tested with various (b) (4) lots. The number of bench scale lots varies among the various tested (b) (4) lots. In one case less than (b) bench scale lots were tested (b) (4) Please provide data for (b) (4) bench scale lots tested using (b) (4) lot and commit to test (b) (4) bench lots for each newly introduced (b) (4) lot.

*Cangene's response to item 1a:*
Cangene's response was reviewed by Dr. Cheng, the statistician, and it was not acceptable. Therefore, she sent an IR that addressed the new term that Cangene has implemented, namely, equivalence acceptance criteria (EAC). The statistical tools that were used in that response regarding the comparison between lots that (b) (4) were also not acceptable. Dr. Cheng is now reviewing Cangene response that was received on 5 February, 2015.

*Cangene's response to item 1b:*
Cangene provided characterization data for the (b) (4) DP lots derived from (b) (4) in sections 3.1 and 3.2 of Appendix 1 in their previous response (Seq. 0040). (b) (4) (b) (4) were not used to manufacture DP, and therefore their characterization is not presented in their complete response to the CR Letter (Seq. 40).

*Reviewers' comment:*
The response is acceptable. Cangene should add the data presented in sections 3.1 and 3.2 of Appendix 1 to the CTD component of the application.

*Cangene's response to item 1c:*
(b) (4) was not used to manufacture DP, and as a result, Cangene did not present this batch's data in their complete response to the CR Letter (Seq. 40).

*Reviewers' comment:*
The response is acceptable.

*Cangene's response to item 1d:*

A description of the procedure to test a new (b) (4) lot, using a (b) (4) as added to section 3.2.S.2.3 *Control of Material*s (page 9) in the CTD component of the application.
The reason that testing of the lab scale runs (b) (4) lot (b) (4) (Table 3 *Comparison of Bench Scale* (b) (4) *Qualifications to Manufacturing-Scale Campaigns* in Appendix 3 in response Seq. 40) was derived from only one run is because only one sample was retained for these tests.

*Reviewers' comment:*
Cangene should provide a complete SOP for Agency review with their exact plan for testing a new (b) (4) lot, which should include (b) (4) testing and other parameters related to rFIX testing.

*FDA IR #2 of 10 December 2014: 29 July 2014 FDA CR item 4*
In your response to CR item #4 you have provided information regarding Chinese Hamster Ovary Host Cell Protein clearance. More information and clarifications are needed as follows:

a. The Agency is concerned about the consistency of the HCP clearance because earlier results showed better clearance than the results reported in the response to the CR letter (b) (4) , respectively). Please provide HCP clearance results for all lots, from lot (b) (4) to the most currently manufactured (b) (4) lot.
b. Please clarify if you are using the same HCP assay in the spiked studies that you used in the testing of commercial lots.
c. According to your report the (b) (4) Please explain then why the use of (b) (4) in the spiking study is the worst-case condition if you aim to examine the (b) (4)
d. You have used two different units in the description of HCP clearance: it is not clear how mg/mL converts to ng/mg.

*Cangene's response to item 2a:*
Cangene presented revised tables of HCP clearance test results for (b) (4) steps (Table 2, 3, and 4 in this submission). These data indicate consistent HCP reduction throughout the overall purification process.

Cangene stated that the high HCP values of (b) (4) , in their complete response to CR letter Item 4, Table 15 (Seq. 40), originated from bench scale HCP spiking studies designed to challenge the (b) (4) and are therefore expected to exhibit higher HCP values when compared to routine manufacturing scale data. The results of Table 5 in this submission show that the (b) (4)

Cangene noted that HCP clearance results in the (b) (4) (Table 4 in this submission) indicate an upward trend over manufacturing runs which aligns with the (b) (4) was used. Cangene committed to execute additional bench scale studies in order to further expand upon the current (b) (4) protocol of this unit operation (e.g. (b) (4) ).

*Reviewers' comment:*
The response is acceptable.
The referral to Table 15 is a typo and it should be corrected to Table 21 of submission Seq. 40.
Tables 2-5 of this submission should be included in the CTD component.

*Cangene's response to item 2b:*
Cangene confirms that the same HCP assay procedure was used in both the spiked studies and in the testing and release of commercial lots.

*Reviewers' comment:*
The response is acceptable.

*Cangene's response to item 2c:*
Cangene recognizes that this study did not examine (b) (4) and was not a representation of the worst case condition. Subsequent to this initial spiking study, additional studies are being executed to further strengthen the design space around this (b) (4) step.

*Reviewers' comment:*
Cangene should submit the results of the studies examining the (b) (4)

*Cangene's response to item 2d:*
Cangene explained the conversion formula from mg/mL to ng/mg and provided a new Table (Table 20) with results expressed in units of ng/mg for the (b) (4)

*Reviewers' comment:*
This information is acceptable. Table 20 of this submission should be included in the CTD component.

**III. Summary and recommendations**

The following Information Requests should be conveyed to Cangene. A response is expected by 26 February, 2015.

1. Your response to Item 1b in amendment Sequence 44 is acceptable. Please include Tables 2-5 of this supplement in the CTD component of the application.
2. You have provided a general description of the lab scale (b) (4) used for testing the new (b) (4) lot. Please provide a complete SOP for the Agency's review with your exact plan for testing a new (b) (4) lot, which should include (b) (4) testing and other parameters related to rFIX testing.
3. Your response to Item 2a in amendment Sequence 44 is acceptable. Please include Tables 2-5 of this supplement in the CTD component of the application.
4. You have confirmed that the validation study regarding CHOP contamination did not examine (b) (4) and was not a representation of the worst case condition. Please submit the results for the studies examining (b) (4) and also include those data in the CTD component of the application.
5. Your response to Item 2d in amendment Sequence 44 is acceptable. Please include Table 20 of this supplement in the CTD component of the application.