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, 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 59 (Sequence 0059; response to the Information Request sent on 10 March, 2015) by Cangene Corporation 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 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). Due to 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 issued for the companion BLA on 1 February, 2013. The clinical hold and CR letters cite CHOP impurities, which elicited antibody development in the 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.

The IRs to the response of 22 December, 2014, item 2, with regard to the CR of 29 July, 2014 items 1, were sent to Cangene on 3 March, 2015, and Cangene sent its response on 12 March, 2015.

This memorandum summarizes the review of the CMC information provided in amendment 59 (Sequence 59), with specific regard to the CR of 29 July, 2014 items 1 and Cangene's responses submitted on 28 October, 2015 and on 12 March, 2015 (response to IR from10 March, 2015).

The Information Requests (IRs) listed below were conveyed to Cangene on 16 March, 2015. Cangene is expected to respond by 20 March, 2015.

II. Review

FDA IR from 10 March, 2015:
In reference to SOP for qualification of (b) (4) lots used for a bench scale (b) (4) (protocol RAW-065-01.5):

1. (b) (4) .
2. (b) (4)

Cangene's response:
Cangene provided a revised SOP for the qualification of (b) (4) lots used for the bench (lab) scale (b) (4) (RAW-065-01.6). The revised version contains the following changes:

(b) (4) .

Reviewers' comments:
The response is not complete. The SOP is silent regarding how to handle a situation in which not all of the testing results can be evaluated due to lack of material. (b) (4)

(b) (4) In Section 8 Qualification Criteria and Performance Targets, Cangene should clarify what is meant by “an assignable cause is not identified” that will still allow a (b) (4) lot to be qualified. In that case Cangene should detail the procedure that will be taken to come to this conclusion.

III. Summary and recommendations

The following Information Requests was conveyed to Cangene on 16 March, 2015. A response is expected by 20 March, 2015.

On March 12, 2015 you provided us with a revised SOP for the qualification of (b) (4) lots used for the bench (lab) scale (b) (4) (RAW-065-01.6). The revised version indicates that the testing applies t (b) (4)

We found the modifications to the SOP to be partially acceptable, but we request the following clarifications:

Please describe in the SOP how you will handle a situation in which not all the testing results can be evaluated because of a lack of material. (b) (4)

Regarding Section 8 Qualification Criteria and Performance Targets, please clarify what is meant by “an assignable cause is not identified” that will still allow a (b) (4) lot to be qualified, and detail the procedure that will be taken to come to this conclusion.