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 47 (Sequence 0048; response to the Information Request sent on 9 January 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 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 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 the Cangene as a 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 November 4, 2014 and Cangene sent its response on November 18, 2014.

An Information Request was sent to Cangene on 9 January, 2015 which originated from February 2013 CR items #12 and 14 to amend the CTD component of the application with new data submitted in these responses. This memorandum summarizes the review of the CMC administrative information provided in amendment 47. No further action is required with regard to this amendment. Cangene updated the CTD component of the application with all the correct data based on the Agency's request.

II. Review

IR # 1:
The rationale for the upper limit of the end of shelf life specification of the (b) (4) is acceptable. However, please include the stability data from the (b) (4) 500 IU/vial DP data (Figure 2 and Table 2 in "response-to-fda-request-dated-november-4") and the paragraph "Rationale for (b) (4) End of Shelf Life Specification" in section 3.2.P.5.6 in the CTD component of the application, because this information is critical for the justification of this limit.

Cangene's response to IR #1:
Cangene's updated CTD component of the application with the stability data from the (b) (4) 500 IU/vial drug product (DP) data (Figure 2 and Table 2 in "response-to-fda-request-dated-november-4") and the paragraph "Rationale for (b) (4) End of Shelf Life Specification".

Reviewers' comment:
The response is acceptable.

IR #2:
All updated results from clearance studies for the following process related impurities: (b) (4) CHO HCP, (b) (4) and the spiking test results for the process-related impurities (including Chinese Hamster Ovary Host Cell Protein (CHO HCP)) should be submitted to the CTD component of the application as shown in section3.2.S.3.2 *Impurities*, page 14-24.

Cangene's response to IR #2*:*
The CTD component of the application has been updated with all the results from clearance studies for (b) (4), CHO HCP, (b) (4) and the spiking test results for the process-related impurities (including CHO HCP).

Reviewers' comment:
The response is acceptable.

IR #3:
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. You have only partially amended the CTD component of the application accordingly; specifically the data in Table 9 in section 3.2.S.2.5 should be amended.

Cangene's response to IR #3:
The CTD component of the application has been amended, specifically the data in Table 9.

Reviewers' comment:
The response is acceptable.

IR #4:
In your response to IR #7 from November 18, 2014, you have provided a new table (Table 5) with the calculated potency regarding all manufacturing lots since 2009 using the IU/vial units. Please amend the CTD component of the application accordingly.

Cangene's response to IR #3:
The CTD component of the application has been amended, specifically with the revised version of report # 20101026-03.

Reviewers' comment:
The response is acceptable.