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 & Leigh Pracht, RPM, HFM-380

From: Chava Kimchi-Sarfaty, Senior Staff Fellow, Chair of BLA 125426/0, CMC Reviewer, Laboratory of Hemostasis (LH), DH/OBRR, HFM-340 & Nobuko Katagiri, Staff Fellow, CMC reviewer, Laboratory of Hemostasis, DH/OBRR HFM-340

Through: Mark Weinstein, Associate Deputy Director, OBRR, HFM–300 &
Timothy Lee, Acting Chief, Laboratory of Hemostasis (LH), DH/OBRR, HFM-392

Subject: Review of CMC information in amendment 18 (Sequence 0019) (responses 1-3 to 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, 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 Cangene's validation of a new (b) (4) n, development of a new sensitive (b) (4) test to demonstrate removal of CHOP), which supports the removal of the CHOP impurities from the product, and their improvement of 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 is a summary of the review of the CMC information provided in amendment 19, with specific regard to CR review items 1-3.

II. Review

Complete Response question 1

With regard to the comparability plan, submitted on October 11, 2012, for drug substance (DS) lots manufactured using the current and modified purification processes, to remove the Chinese Hamster Ovary (CHO) cell-derived host cell proteins (HCP), please provide the following:

a. (b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

[redacted]

Reviewers' comment:

(b) (4)

[redacted]

Complete Response question 2

In your response to our Information Request dated July 25, 2012, you reported an approximate (b) (4) recognition of HCP by the (b) (4), as determined by comparison of the (b) (4) analysis. We consider this level of HCP coverage

by the (b) (4) to be insufficient, and a potential cause for the under-estimation of HCP levels in the DS of IB1001. Therefore, please improve the (b) (4) for HCP by using (b) (4)

Cangene response to CR 2:
Cangene's response to Item 2 is provided in Appendix 2 (Response to CR Letter CMC Item 2).

Reviewers' comment:
Appendix 2 contains the same information that was provided by Cangene in their response to the hold letter. The response was reviewed previously by this reviewer and summarized in review memo dated 25 July, 2013 and is satisfactory.

Complete Response question 3
With regard to the testing of (b) (4) please provide the following data for the (b) (4)

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(b) (4)

Cangene response to CR 3b:
(b) (4)

2 pages determined to be not releasable: (b)(4)

(b) (4)

:

(b) (4)

III. Summary and Recommendations

The Information provided by Cangene is generally satisfactory, but not complete. Therefore, we recommend conveying to Cangene the following Information Request. Please request Cangene to respond by 5 May, 2014.

1. (b) (4)

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