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 and IND 13551 & Leigh Pracht, RPM, HFM-380

From: Chava Kimchi-Sarfaty, Senior Staff Fellow, CMC Reviewer, Laboratory of Hemostasis (LH), DH/OBRR, HFM-340

Through: Mahmood Farshid, Deputy Director, Division of Hematology, HFM-300,
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 (viral removal/inactivation) in amendments 15 -19 (including the response to CR letter) by Cangene – Coagulation Factor IX (Recombinant) [IB1001]

I. Background and summary

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 will 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. Based on the information Cangene provided (mainly validation of a new (b) (4) and new sensitive (b) (4) test to demonstrate removal of CHOP), which supports the removal of the CHOP impurities from the product, and the improvement of the specificity and sensitivity of the assays for CHOP, the clinical hold was lifted on 26 July, 2013.

Cangene's response to the clinical hold on 5 July, 2013 and Type A meeting request from 11 September, 2013 (which was canceled on 20 September, 2013) includes additional CMC information about the rFIX, unrelated directly to the clinical hold. Cangene responded to the CR letter on 28 January, 2014. This memorandum is a summary of the review of the CMC information provided in amendments 15-19, with specific regard to the viral removal/inactivation.

II. Review

II a. Materials of biological origin

Table 1 of amendment 19 (copied below) details the biological origin components used in the manufacturing of IB1001 DS, the supplier and step in which they are used. There are no raw materials of human origin used in the manufacture of rFIX. There are also no raw materials of animal origin that

are used directly in the commercial manufacturing process (b) (4)

(b) (4)

II b. Adventitious agent safety of the cell lines and cell banks

The host cells are a (b) (4) Chinese Hamster Ovary (CHO) cell line, (b) (4)

Extensive testing was performed to assure adventitious agent safety of the listed cell banks, including the (b) (4)). Table 2 of amendment 19 lists the results of the cell testing. Testing was performed by (b) (4)

(b) (4)

.

Reviewer comment: the results are satisfactory.

II c. Production process - adventitious agents safety evaluation

IB1001 drug substance is manufactured in a recombinant Chinese Hamster Ovary (CHO) cell line. As for any biological material and specifically for CHO cells, there are risks of contamination with adventitious viruses, (b) (4)). In addition, CHO cell lines express retrovirus like particles (RVLP). The purification process includes two specific steps, solvent/detergent (S/D) treatment and nanofiltration, for virus removal/virus inactivation.
To address the FDA's concerns and to assure an acceptable safety factor for viral removal, the following changes in the manufacturing process were implemented and validated:

(b) (4)

Figure 1 of section *32a2.advertitious agents safety evaluation* contains an overview of the manufacturing process. The highlighted steps were validated for viral inactivation/removal:

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