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: Final review of Biologics License Application by Cangene Corporation for Coagulation Factor IX (Recombinant) [IXINITY™, formerly IB1001] expressed in Chinese Hamster Ovary cells

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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. IXINITY™ is indicated in adults and children ≥ 12 years of age with Hemophilia B (congenital FIX deficiency) for (1) control and prevention of bleeding episodes and (2) perioperative management. IXINITY™ is not indicated for induction of immune tolerance in patients with Hemophilia B, and cannot be marketed for routine prophylaxis treatment of patients with Hemophilia B as another currently licensed Recombinant Coagulation FIX (rFIX) has received orphan drug exclusivity for the prophylaxis indication.

This biologics license application (BLA) for Coagulation Factor IX (Recombinant) was reviewed by a committee that included the following CBER reviewers:
Dr. Iftekhar Mahmood (Clinical Pharmacology), Dr. Lisa Stockbridge and Dr. Loan Nguyen (Advertising and Labeling), Dr. Michael Wyatt (former reviewer) and Dr. Anne M. Pilaro (Pharmacology/Toxicology), Ms. Karen Campbell and Dr. Lokesh Bhattacharyya (Lot Release/Analytical Methods), Mr. Edward Thompson and Ms. Leigh Pracht (former RPM) (Administrative/ Regulatory), Dr. Rabia Ballica and Dr. Deborah Trout (CMC/Facility), Dr. Roman Drews (Former Chair of Review Committee and CMC/Product), Ms. Carla Jordan (Bioresearch monitoring), Dr. Bethany Baer (epidemiology), Dr. Nisha Jain, Dr. Irwin Feuerstein and Dr. Stephanie Omokaro (former Clinical reviewer) (Clinical), Ms. Carla Jordan (Bioresearch monitoring), Dr. Nobuko Katagiri and Dr. Hyesuk Kong (CMC), Dr. Chava Kimchi-Sarfaty (Current Chair of Review Committee and CMC), and Dr. Chunrong Cheng (Biostatistics).

A detailed review memo (attached) was submitted by Dr. Roman Drews, the former Chair of this BLA, which provides an introduction regarding Hemophilia B, describes the structural features of the rFIX molecule, and supports the manufacturing process. Further his review defines the established process controls, and drug substance manufacturing process, and provides a complete characterization of the drug substance, including physicochemical characterization of rFIX. The review communicates a detailed description of other parameters of the drug substance and drug product attributes such as impurities, control strategy for quality testing, justification for the proposed release specification, process validation, drug product attributes, pharmaceutical development and specification of the drug product. Other sections of the review describe and support the manufacturing process and established process controls for drug product, the analytical procedures that are used for the (b) (4) drug product,

method validation and reference standards, adventitious agents safety evaluation, container closure system and stability.

Chemistry, Manufacturing, and Controls critical issues that were discussed and resolved during BLA review

Implementation of a new (b) (4) *test to detect Chinese Hamster Ovary proteins (CHOP)*

Inspiration, the former sponsor for IND 13551, in the second quarter of 2012, found that a higher than expected number of subjects (23% of the subjects) developed antibodies against host cell proteins (HCPs) from Chinese Hamster Ovary (CHO) cells, which were employed to produce the drug substance. The major CMC deficiencies cited in the Complete Response (CR) letter issued for the companion BLA on 1 February, 2013 and were related to the CHO protein (CHOP) impurities, which elicited the development of antibodies in study subjects.

As part of the response to the CR letter (dated 27 January, 2014), which cited CHOP impurities, Cangene validated a new (b) (4) and developed a new sensitive (b) (4) test for CHOP, which supports the removal of the CHOP impurities from the product. Although non-inhibitory antibodies to FIX are observed in subjects receiving the modified version of the product (see the final clinical reviewer memo), no clinical consequences have been observed. The previous version of the drug is referred to in this document as former-IXINITY™ while the modified version, after the implementation of the (b) (4), is referred to in this document as modified-IXINITY™. Three former lots and three modified process lots were used for comparability studies between the former process and the modified process, and the comparability of the modified drug was established at the biochemical level (b) (4) lots of modified-IXINITY™ were manufactured after the implementation of the modification process. Their attributes were reviewed and found to be comparable to those of former-IXINITY.

Resolution of inspectional issues

Validation of (b) (4) *testing in* (b) (4) *lots used for* (b) (4) *and establishment of a new test procedure of* (b) (4) *lots that are used for* (b) (4)

On (b) (4) the Agency inspected (b) (4) a contracting site for the manufacture of the drug substance. During the inspection, FDA found that beginning in September 2013, four out of (b) (4) production lots of Coagulation FIX were (b) (4) Cangene's incomplete response to the FDA Form 483, that mainly concerned (b) (4) problems, and their incomplete response to Information Requests (IRs), led to the issuance of a CR Letter on 29 July, 2014. Cangene responded to this CR letter on 28 October, 2014 with information regarding the investigation of the (b) (4) problem, and a description of the modifications in the testing procedure of the (b) (4) lots that are used for the (b) (4), detailed as follows:

(b) (4)

(b) (4) Lots manufactured after the issue of (b) (4) was resolved, were assessed for their quality, purity and potency, and were found to be satisfactory.

Establishment of in-process controls that reflect manufacturing capability

The in-process specifications that Cangene originally proposed lacked justification for the proposed control strategy for each unit operation, and therefore, were considered to be inadequate for proper routine, commercial process control. The Agency requested that Cangene provide summaries of relevant data, gathered during the developmental and qualification stages of process validation, to demonstrate their scientific understanding of each unit operation in terms of its performance and control strategies. In Amendment 18 (Sequence 0019) dated 17 January 2014, Cangene provided results of a complete review of the Process Control Strategy for defining and classifying the Manufacturing Process Parameters according to (b) (4). As a result of this review, the Agency accepted a new Process Control Strategy based upon risk assessment, which replaced a Failure Mode Effects Analysis risk assessment tool, and a Risk Priority Number designation for determining Critical Process Parameters.

Establishment of release specifications which support clinical use, clinical safety, product quality, and the validated manufacturing process

Some of the proposed acceptance criteria for (b) (4) drug product release and stability specifications, including parameters regarding impurities, (b) (4), potency, and purity, were either not identified or the ranges were too broad, and not fully representative of the release test results. The Agency requested that Cangene set the acceptance limits based on historical data. Cangene complied, and the Agency accepted the new and narrower acceptance criteria and in-process limits that Cangene proposed.

Assessment of (b) (4) *of rFIX*

(b) (4)

To support licensure for the proposed indications, the clinical development program included a multi-phase 1/2/3 clinical trial (IB-1001-01) consisting of (1) PK phase: a randomized, double-blind, single-dose, crossover, pharmacokinetic comparison between IXINITY™ and a previously licensed rFIX product with an optional repeat PK study; (2) treatment phase: a non-randomized, open-label study of safety and efficacy; (3) a continuation phase study of long-term safety and efficacy; (4) a surgery sub-study with bolus or continuous infusion; and (5) a modified phase defined by FDA as a continuation phase after the introduction of a modified form of IXINITY™. There is also an ongoing pediatric trial (IB-1001-02) of the modified-IXINITY. Some preliminary data from the ongoing pediatric trial are discussed in this SBRA; however, the final study report is still pending.

In this review cycle, the reviewers conclude that all the deficiencies listed above have been adequately addressed.

Research by Advertising and Promotional Labeling Branch (APLB) indicates that the proposed proprietary name IXINITY is acceptable.

I. Summary and recommendations

It is recommended that IXINITY™ be approved for use in adults and children ≥ 12 years of age with Hemophilia B (congenital FIX deficiency) for:

- Control and prevention of bleeding episodes
- Perioperative management

The manufacturing process for IXINITY™ is considered validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the commercial product which meets acceptable release specifications. Inspectional issues were adequately addressed. The reviewers from the Division of Hematology Research and Review, and the Division of Manufacturing and Product Quality both conclude that Cangene has provided sufficient data and information on chemistry, manufacturing, and controls to support the licensure of IXINITY™.

Outstanding issues from previous review cycles have all been resolved, and all reviewers unanimously recommend approval of 125426/0 BLA for Coagulation Factor IX (Recombinant) [IXINITY] expressed in CHO cells.