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, Chemist, Chair of BLA 125426/0, CMC Reviewer, Laboratory of Hemostasis (LH), DHRR/OBRR & Nobuko Katagiri, Research Biologist, CMC reviewer, Laboratory of Hemostasis, DHRR/OBRR

Through: Mark Weinstein, Associate Deputy Director, IOD/OBRR
Timothy Lee, Acting Chief, Laboratory of Hemostasis (LH), DHRR/OBRR

Subject: Mid-cycle meeting summary for Coagulation Factor IX (Recombinant) [IXINITY™, formerly IB1001]

I. CMC background and summary; discussed by Chava Kimchi-Sarfaty

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.

IXINITY™ primary amino acid sequence is identical to that of the Thr148 allelic form of plasma derived FIX. Similarly to native FIX, IXINITY™ is composed of (b) (4) .

(b) (4)

Manufacturing:
All validation studies related to the manufacturing of IXINITY™ were completed, including (b) (4) . The manufacturing process is discussed in Figure 1.

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 and that the antibodies occurred in 23% of the patients that received the drug. The antibodies were shown to target host cell proteins (HCPs) in Chinese Hamster Ovary (CHO) cells (Chinese Hamster Ovary protein, CHOP). 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 were related to the CHOP impurities, which elicited the development of antibodies in study subjects.

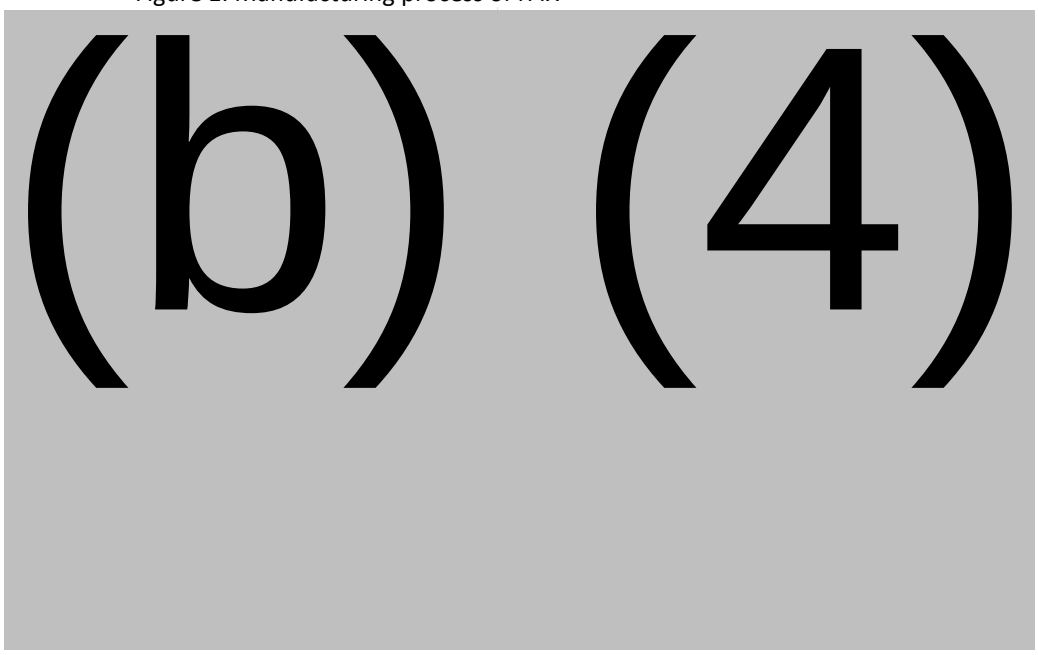
Response to the CR letter (Cangene responded to the first clinical hold on 5 July, 2013, and responded to the CR letter on 28 January, 2014) included the following items:

- Cangene implemented a new (b) (4) HCP specification of (b) (4) represents a (b) (4) reduction in HCP levels compared to the former process as measured by the new CHO HCP (b) (4).
- (b) (4)
- (b) (4) .
- (b) (4) more sensitive to detecting a wider spectrum of CHOP by using (b) (4)
- The primary components of HCPs were identified
- Rabbit study to detect anti-CHOP antibodies

Dr. Epstein discussed how we could have prevented the CHOP contamination and how we should review other products that are made in CHO cells regarding tools that examine the level of CHOP contamination. Currently, the commercial (b) (4) kit is used often at the IND stage. We might consider adding a request for sera from individuals that developed antibodies against host cell proteins (HCPs) in Chinese Hamster Ovary (CHO) cells.

Dr. Pilaro discussed the pros and cons of the use of animal models for these studies, but emphasized that the rabbit study, conducted by Cangene as a result of the hold, revealed no antibodies to CHOP in materials purified through the new process. Based on Dr. Mahmood's report, despite not having a full PK study conducted after the introduction of the new (b) (4) due to the scarcity of newly treated individuals, one can still show comparability of the PK; he is satisfied with this data. CMC also reported that they were satisfied by the results from comparability studies conducted after the manufacturing change.

Figure 1. Manufacturing process of rFIX



Product Characterization:
All validation studies regarding product characterization were completed, and the proposed acceptance limits for the (b) (4) DP release specifications were narrowed satisfactorily.

- The potency of the reference material and several batches of rFIX used in clinical studies has been determined in early stages of production through an inter laboratory study performed at

three international laboratories versus the 4th International Standard for Blood Coagulation Factor IX Concentrate.

- (b) (4) : recently the instrument was changed from the (b) (4) analyzer and the estimated potency using the new instrument is about (b) (4) less than that reported by Cangene's contractor (b) (4) Cangene is using the new assay results for filling.
- Activity of rFIXa was monitored at (b) (4) DP release by the (b) (4) assay

Dr. Jain suggested a PMC field study to evaluate the ability of clinical laboratories to monitor recovery of their product in patient plasma (post-infusion monitoring) using their routine assays and reagents.

Cangene's incomplete response to the FDA Form 483, regarding observations cited during the (b) (4) inspection o (b) (4) , their incomplete response to an Information Requests 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. The main problem that arose during that inspection was (b) (4) of lots manufactured between August 2013 and June 2014. Cangene responded to this CR letter on October 28, 2014.

There are no CMC issues that may hold up approval; however there are still a few issues that CMC is discussing with Cangene regarding (b) (4)

1. SOP to examine new (b) (4) lots
2. Is there a correlation between (b) (4) ? Statistical analysis was not performed satisfactorily and the statistician is waiting for Cangene's response.

The labeling was not yet complete; in addition to changes suggested by several disciplines, Cangene will be asked to incorporate new sections from the labeling of the last two rFIX products approved by the Agency.

II. Clinical background and summary; discussed and written by Irwin Feuerstein

Data were presented from the pivotal phase 1/2/3 study that included 77 subjects on prophylaxis, on-demand treatment, or undergoing major surgical procedures. Data were also discussed from an ongoing pediatric trial with data available for nine subjects. The clinical development program for IB1001 (IXINITY) included a comparative PK study against BeneFIX, a non-randomized open-label treatment phase where subjects received either prophylaxis or on-demand for at least 50 exposure days (ED) with option for continuation phase, and a perioperative management substudy. Because of orphan exclusivity by another product, a prophylaxis indication cannot be claimed, and only treatment of bleeding and perioperative management were discussed further. Additional safety and immunogenicity data from the current version of the biologic were submitted after modification of manufacturing with an additional (b) (4) step. The primary CHO antigen before addition of this (b) (4)

Efficacy was demonstrated for treatment and prevention of bleeding episodes and for perioperative management. The PK Phase and Repeat PK Study with the original product demonstrated noninferiority to marketed product and no deterioration in recovery. Performance for the treatment of bleeding episodes was acceptable as reported by investigators and subjects. Bleeding resolved in 71% of episodes (360/508) with a single infusion and in 13% (66/508) after two infusions. Hemostatic efficacy for on-demand treatment of bleeding was rated by subjects as excellent or good in 84% of treated bleeding episodes. The Surgery Substudy demonstrated target levels for factor IX, acceptable performance as assessed by investigators, and outcomes as expected or better than expected in every procedure. Blood loss was as expected or less than expected in all surgical procedures.

A total of 77 subjects were enrolled in one or more study phases of Trial IB1001-01 and 68 of these subjects were used for analysis of safety in the treatment phase. No deaths were reported. There were 14 serious adverse events, all considered unrelated. The most commonly reported non-serious adverse events and reactions were typical for the class and were acceptable. The only adverse reaction reported in more than one subject was headache. Some subjects exhibited allergic symptoms, but those subjects

had pre-existing allergy and the allergy had no temporal relationship to the development of antibodies. There were no instances of anaphylaxis or nephrotic syndrome. No subject developed inhibitory antibody to factor IX at any time, in any phase of the trial. Non-inhibitory antibodies to factor IX developed in approximately 30% of subjects in IB1001-01, with no clinical consequences. In ongoing pediatric study IB1001-02, 33% of subjects have developed non-inhibitory antibodies to factor IX. The significance of noninhibitory antibody in this and other products is unknown. The safety profile of the current version of the product is similar to that tested in the clinical trial, with no inhibitor development and similar spectrum of adverse experiences. It remains to be determined how much of the data from IB1001-02 will be included in the review and labeling. Non-inhibitory antibodies to factor IX continue to be seen in the current version of the product, with no clinical consequences.
Ongoing immunogenicity assessments for anti-CHOP antibody formation have revealed no subject with transition from negative to positive with the current version of the product. Most subjects who were positive at transition have shown decreasing titers.
Regarding the matter of prior and current product in labeling, some members were of the opinion that it was better to not dwell on a product that no longer exists, and focus on the current product.
Comparability testing between previous and current product showed no significant differences in laboratory and animal assessments, so a repeat efficacy trial was not requested. The product team mentioned that adding a (b) (4) as was done here would not trigger the need for a new clinical efficacy trial. The SBRA and clinical memo should include description and discussion of the issues that lead to development of the current product. However, to include such information in the prescribing information would likely be confusing and unhelpful for the prescribing clinician, so the prescribing information will focus on the marketed biological drug product. The application has been approved by PeRC.

iii. Additional comments by other disciplines

Rabia Ballica from DMPQ noted that the inspection report cannot be completed prior to CMC confirmation that Cangene responded satisfactorily to all 483 items. CMC is working with the statistician to evaluate Cangene's response regarding correlation between (b) (4)

Quality Control (Campbell) tests will be performed for two lots manufacturing after June 2014 (post-encounter of (b) (4) by Cangene).

Epidemiology (Baer), DB (Cheng), BIMO (Jordan), clinical pharmacology (Mahmood) and Pharm/Tox (Pilaro) have completed their review and have no further comments.

Labeling (Nguyen) was not presented at the meeting, but earlier she indicated that she is in the last stages of review.