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

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

Subject: Review of CMC information in amendment 61 (Sequence 0060; response to the Information Request sent on 4 March, 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 the 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 host cells employed to produce IB1001 drug substance (DS). Due to 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 issued for the companion BLA on 1 February, 2013. The clinical hold and CR letters cite CHOP impurities, which elicited antibody development in the study subjects, as the main source of concern. 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) ; their development of a new sensitive (b)(4) test for CHOP that excludes CHOP impurities from the product; and their improved specificity and sensitivity in assays for evaluating 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 Cangene as the 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.

This memorandum summarizes the review of the CMC information provided in amendment 61 (Sequence 60), with specific regard to the Agency's request that a field study be conducted to evaluate the ability of clinical laboratories to monitor recovery of the product in patient plasma (post-infusion monitoring) using their routine assays and reagents. Cangene's response is satisfactory and below is the Agency's response.

II. Review

FDA IR from 4 March, 2015:
Cangene Corporation commits to perform a field study to evaluate the ability of clinical laboratories to monitor recovery of products in patient plasma (post-infusion monitoring) using their routine assays and reagents. Please propose a start date (month and year) in the PMC agreement.

Cangene's response:
Cangene provided the NIBSC study, in which the monitoring of activity for IXINITY has been assessed at 17 laboratories using routine assays including the one-stage clotting assay with multiple reagents (b)(4) and routine reagents at each test site) and the (b)(4) assay using two standard kits. Cangene indicated that these tests are commonly used to test clinical samples, and therefore these tests remain relevant for plasma samples during post-infusion monitoring. The test results for IXINITY were consistent with other recombinant products (e.g. R1 and R2, IXINITY is labeled R3) and standards in both assays, such as NIBSC recombinant FIX reference and the 4th International Standard for FIX Concentrate; for example see Tables 4b and 5b of the report:

Table 4b Geometric Mean (GM) and inter-laboratory coefficient of variation (GCV) for R1 (Pink), R2 (Orange) and R3 (Purple), against S1, the 4th IS, Concentrate

	R1 (Pink)			R2 (Orange)			R3 (Purple)		
Method	N	GM (IU/ml)	GCV	N	GM (IU/ml)	GCV	N	GM (IU/ml)	GCV
(b)(4)	15	9.5	8.1%	15	10.3	9.0%	15	9.6	8.1%
	16	9.6	9.6%	16	10.3	10.4%	16	9.8	8.3%
	15	6.9	5.8%	15	6.9	6.0%	15	7.1	5.2%
	11	7.3	6.2%	11	7.7	9.3%	11	7.5	8.8%
	11	6.4	13.6%	11	6.6	17.1%	11	6.8	11.8%
	3	8.6	20.6%	3	9.0	26.0%	3	8.7	19.8%
	2	6.8	NA	2	7.1	NA	2	7.1	NA
	5	7.8	20.6%	5	8.2	24.0%	5	8.1	18.8%

Table 5b Geometric Mean (GM) and inter-laboratory coefficient of variation (GCV) for R1 (Pink), R2 (Orange) and R3 (Purple), against S2, the NIBSC Recombinant FIX reference preparation

	R1 (Pink)			R2 (Orange)			R3 (Purple)		
Method	N	GM (IU/ml)	GCV	N	GM (IU/ml)	GCV	N	GM (IU/ml)	GCV
(b)(4)	15	8.6	5.5%	15	9.3	6.9%	15	8.8	5.2%
	16	8.7	5.4%	16	9.2	5.3%	16	8.8	4.4%
	14	9.0	3.9%	15	9.0	4.9%	15	9.1	4.1%
	11	8.8	2.4%	11	9.3	7.2%	11	9.1	5.3%
	11	8.5	10.6%	11	8.9	13.6%	11	9.1	8.4%
	3	8.8	2.4%	3	9.2	1.7%	3	8.9	2.0%
	2	8.6	NA	2	9.1	NA	2	9.1	NA
	5	8.7	2.2%	5	9.1	2.0%	5	9.0	1.9%

Cangene suggested that post-infusion monitoring of the IXINITY levels in patient samples at clinical laboratories are expected to be similar to those observed for the current marketed recombinant factor IX products. "Cangene requests that the FDA evaluate the provided data to determine whether this report provided sufficient information to address the request for a field study."

Reviewers' comments:

Similar to the two other recombinant FIX products tested in this study, IXINITY (R3) demonstrated an agreement with regards to potency when tested by both the one stage clotting assay (all reagents) and the (b)(4) assay kits when compared to the recombinant FIX reference material (S2). The variability is similar to other products, sometimes even lower when compared to the standards.
Based on consultation with Drs. Tim Lee and Nisha Jain, we propose to accept Cangene's response and allow Cangene at this juncture, to forego the field study. We may re-visit this decision in the future if their data suggests that such comparison will be beneficial. Additionally, the Package Insert should contain information on the variability of test results due to differences in assay reagents and reference standards.

III. Summary and recommendations

The following response should be conveyed to Cangene:

As a response to the Agency Information Request from 4 March, 2015, you have reported in BL STN 125426/0, Amendment 61, Sequence 60 of the NIBSC study, that the monitoring of activity for IXINITY has been assessed at 17 laboratories using routine assays including the one-stage clotting assay with multiple reagents (b)(4) and routine reagents at each test site) and the (b)(4) assay using two standard kits. Based on the data, we agree that at this point that a field study is unnecessary. We may re-visit this decision in the future if the data suggests that such study and comparison will be beneficial. Additionally, the Package Insert should contain information on the variability of test results due to differences in assay reagents and reference standards.