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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Subject: Review of CMC information in amendment 54 (Sequence 0055; response to Information Request discussed during teleconference held on 20 February, 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). 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 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) ; development of a new sensitive (b) (4) test for CHOP, which supports the removal of the CHOP impurities from the product; and their improvement in the specificity and sensitivity of the assays for 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.

The IRs to the 1 February, 2013 Complete Review items 10, 11, 12 and 14 were sent to Cangene on 4 November, 2014, and Cangene sent its response on 18 November, 2014. The IRs to the 28 October, 2014 Complete Review items 1-6 were sent to Cangene on 10 December, 2014, and Cangene sent its response on 22 December, 2014 as Amendment 43 (Sequence 44).

The IRs to the response of 22 December, 2014, with regard to the CR of 29 July, 2014 items 1 and 4, were sent to Cangene on 11 February, 2015, and Cangene sent its response on 26 February, 2015.

This memorandum summarizes the review of the CMC information provided in amendment 54 (Sequence 55), with specific regard to the CR of 29 July, 2014 item 1 and the teleconference that was held on 20 February, 2015. The review on the items summarized in this amendment is complete and Cangene's response is satisfactory.

II. Review

FDA requests to provide data in support of the (b) (4) *manufacturing process*

In Cangene's response to the CR letter regarding lots at or near the cut-off limit for (b) (4), the company provided an assessment of manufacturing lots including a comparison to several lots manufactured at (b) (4) This partial assessment was provided earlier in tables and graphs using statistical tools to analyze and present the data, but Chunrong Cheng, the FDA statistician, found that the statistical tools that were used are not acceptable. Therefore, a teleconference was conducted on 20 February, 2015 to request Cangene to send the raw data of (b) (4) of all lots at or near the cut-off limit for (b) (4). The aim is to look for any trends in (b) (4) that might be associated with (b) (4). Attachment 1 of this amendment (sequence 55) includes the requested information.

The following parameters were provided:

- (b) (4)
- For Drug Product (DP): Potency, (b) (4) reconstitution time, residual moisture (b) (4), mannitol, trehalose, polysorbate 80, appearance, sterility and endotoxin.
- (b) (4)
- (b) (4).
- The following batches from the original manufacturing process (since discontinued) were included: (b) (4)
- The following rejected batches were included: (b) (4)
- The following terminated batches were included: (b) (4)
- Table 3 includes the (b) (4) batches
- The following DP lots (500 IU/vial) were included in the repor (b) (4)

- DP lot, (b) (4) (500 IU/vial) that originated from (b) (4) was included in the report.
- The following DP lots (1000 IU/vial) were included in the report (b) (4)
- The following DP lots (1500 IU/vial) were included in the report (b) (4)
- The following DP lots (1500 IU/vial) were included in the report (b) (4)

Reviewers' comment:
Some results are not reported for some of the lots because the test method was changed, or was not part of the release panel at the time the lot was manufactured. At earlier stages of production Cangene did not test the (b) (4)
No trends or association can be detected between (b) (4). The response is acceptable.

FDA requests an update on Observation 2 of (b) (4) *FDA 483 and related response to Item #10 of Cangene Complete Response Letter.*
FDA FORM 483 OBSERVATION ITEM 2: Results obtained in the QC laboratories were invalidated without adequate investigation. For example, Assay 12A013, file 414A0161- the assay acceptance criteria were not met and the assay was categorized as invalid.

The procedures for investigation of invalid assays were strengthened by updating the governing procedures, which include the *Invalid Assay Handling Procedure* (QC-1207), and *Laboratory Investigation Procedure* (GMP-0401). These revisions ensure that no repeat sample testing can be performed without documented justification and management approval. Tracking of invalid assay metrics is included in the Quarterly Management Review (QMR) to ensure appropriate actions are taken for any observed adverse trends. Subsequent to the procedure revisions, all QC analysts and managers have undergone training on the revised procedures. The following additional documents were provided to support the response:

1. Attachment 2: QC Laboratory Investigation Report (Phase 1 Investigation)
2. Attachment 3: training forms
3. Attachment 4: Invalid Assay Trending

Reviewers' comment:
The response is acceptable and complete.

FDA requests an update on Observation 5 of (b) (4) *FDA 483 and related Response to Item 11 of Cangene Complete Response Letter concerning the assignment of expiry dates and execution of stability assessments on laboratory reagents. The update should include additional rationale on why reagents used within* (b) (4) *are not intended to be studied during reagent stability studies.*
FDA FORM 483 OBSERVATION ITEM 5: No stability studies were conducted on reagents in the QC laboratories.

Cangene reported that the SOP *Qualification and Validation of Analytical Procedures* (GMP-1246) was revised to require that, as part of method validation, stability criteria be established for all critical reagents for validated methods. Critical reagent stability studies include evaluation of expiration dates after opening, bench stability during testing and overall assigned expiration dating as appropriate. Cangene provided a list of all the critical reagents and the criteria to include reagents in this list. In the meanwhile, before the stability testing is complete, critical reagent expiry dates have been revised based upon historical assay performance. Test methods were revised to incorporate detailed descriptions on reagent preparation, storage and handling.
The following additional documents were provided to support the response:

1. Attachment 5: critical reagent inventory tracking log
2. Attachment 6: control chart use for quality control

Reviewers' comment:
The response is acceptable.

III. Conclusions

The review of the items summarized in this amendment is complete and Cangene's response is satisfactory. No association was detected between (b) (4) . Cangene responded satisfactorily to several items that had remained open since their last response to the 483 FDA items.