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 & Leigh Pracht, RPM, HFM-380

From: Chava Kimchi-Sarfaty, Senior Staff Fellow, Chair of BLA 125426/0, CMC Reviewer, Laboratory of Hemostasis (LH), DH/OBRR, HFM-340 & Nobuko Katagiri, Staff Fellow, CMC reviewer, Laboratory of Hemostasis, DH/OBRR HFM-340

Through: 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 in amendment 18 (Sequence 0019; responses 4-9 to the CR letter) by Cangene – Coagulation Factor IX (Recombinant) [IXINITY™, formerly IB1001]

I. Background and summary

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.

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 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, 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 clinical hold on 5 July, 2013 and responded to the CR letter on 28 January, 2014. This memorandum summarizes the review of the CMC information provided in amendment 18, with specific regard to CR items 4-9. We have consulted with Dr. Nancy Kirshbaum (LH, DH) regarding Cangene's response to CR item 5 and CR item 7. Mahmood Farshid, Deputy Director, DH concurs with the assessment of CR item 8 that deals with viral inactivation.

On 6 March, 2014 Emergent BioSolutions informed the Agency that Cangene is now a wholly-owned subsidiary of Emergent BioSolutions.

The Information Requests listed below should be conveyed to Emergent BioSolutions. Emergent BioSolutions is expected to respond by April 30.

II. Review

Complete Response Item 4

You stated in Section Overview of Process Validation Studies (3.2.S.2.5.1):
"A Parameter Justification Report was generated for each unit operation. The report summarizes in a single document how the commercial manufacturing parameter ranges were defined and where process development and/or characterization reports primarily justify parameter set points and ranges. In general, process parameters ranges are deduced from scientific principles, defined equipment tolerances and/or sourced from historical clinical GMP runs and characterization studies. Likewise, performance parameter ranges (e.g. In-process Limits, In-process Controls, and In-Process Specifications) are deduced from scientific rationale, statistical analysis of historical batch performance, and/or known process outcomes required to achieve the defined (b) (4)

However, you have not provided scientific evidence to demonstrate that the manufacturing process is capable of consistently producing quality product and have not justified the proposed control strategy for each unit operation. Specifically, you have not demonstrated an understanding of the causes of process variations, an ability to detect the variations, and an assessment of the potential impact of variations on the process and product quality attributes.

Therefore, please provide summaries of relevant data gathered during the developmental and qualification stages of process validation that demonstrate your scientific understanding of each unit operation regarding its performance and control strategies. Justification of the proposed operating ranges should include, but not be limited to, a short description of the analytical methods used to monitor each unit operation, a summary of the results, and an assessment of the potential impact of a variation on process performance and quality attributes of your product.

Cangene response to CR Item 4:
The Process Validation, Manufacturing Process and Process Controls and the Control of Critical Steps sections in Cangene's BLA have undergone significant revision since the original Inspiration BLA submission and are now more accurately reflect both the process and process controls. Cangene provided the following information:

- Results from process validation runs demonstrating the performance and controls over the individual unit operations (Section 3.2.S.2.5)
- Definition and justification of the determination of acceptance limits and operating ranges (Section 3.2.S.2.2)
- Critical process parameters and Critical Quality Attributes (CQAs) (Section 3.2.S.2.4).
- A summary of the critical parameters per unit operation, the analytical methods and operating ranges used to monitor these parameters, a snapshot of the trended results from manufacturing scale batches, and an assessment of the potential impact of a variation on process performance and quality attributes (Table 16).
- Descriptions and/or references to analytical methods for in-process monitoring (Table 17). This includes (b) (4) . This table does not include other analytical methods used in in-process testing such as (b) (4) as described in Section 3.2.S.4.1
- Process validation for IB1001 manufacture: a complete review of the Process Control Strategy was performed for defining and classifying the Manufacturing Process Parameters according to (b) (4) . As a result of this review, the Failure Mode Effects Analysis (FMEA) risk assessment tool and Risk Priority Number (RPN) designation for determining Critical Process Parameters (CPPs) were replaced with a new Process Control Strategy based upon risk assessment that evaluates every parameter's contribution to variation in the process.

- As an outcome of the Process Control Strategy review, the followings steps were performed:
  a) Policies were created and made effective for Process Design, Process Performance Qualification (PPQ), and Continued Process Verification (CPV). Process Design includes the new definition of CPP that is aligned with the ICH Q8 Guidance; definitions for Process Parameter(s), Critical Process Parameter (CPP), Critical Quality Attribute (CQA), Key Operating Parameter (KOP), In-Process Limit (IPL), Normal Operating Range (NOR), Proven Acceptable Range (PAR), and Characterized Range.
  b) A Risk Assessment Mitigation Matrix (RAMM) was designed to assess the manufacturing process for critical parameters according to (b) (4) .
  c) Criticality of the impact of variations on process performance and quality attributes of the product was determined based upon historical data from bench scale and GMP manufacturing batches.
  d) The Process Control Strategy was revised based on the output of the RAMM.
  e) A life-cycle approach is now utilized for CPV (Section 3.2.S.2.5). All parameters, limits and ranges are re-evaluated (b) (4) documented in an (b) (4) Report, which is consistent with the ICH Q8 guidance.

Reviewers' comment:
This information is not complete. Table 17 does not contain other analytical methods used in in-process testing described in Section 3.2.S.4.1. Cangene should list all the analytical methods employed in in-process testing including, but not limited to, (b) (4) in this table. The Agency requests that (b) (4) tests be included in several steps during the drug substance manufacturing process (please see item 5).

Complete Response Item 5:

With regard to the in-process controls for the (b) (4) , please include Acceptance Limits for the following in-process control parameters:

(b) (4)

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Cangene response to CR 5a:
Cangene provided the following information:

(b) (4)

Cangene stated that the (b) (4) is measured by (b) (4) during routine manufacturing, with an in-process limit of (b) (4)

Reviewers' comment:
Based on the nomenclature system of the lots, Cangene provided information regarding (b) (4) lots that were probably manufactured during the Former Process. Since Cangene implemented the main change in the Modified Process (b) (4) , it is acceptable to review information obtained from these lot. However, Cangene provided the (b) (4) . It is acceptable to us (b) (4) drug product release (b) (4) and the manufacturing process narrative should also include the basis by which final product vials are filled by activity units. In addition, for the justification

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

(b) (4)

Reviewers' comment:
The response is complete.

III. Summary and Recommendations

The Information provided by Cangene is generally satisfactory, but not complete. Therefore, we recommend conveying to Cangene the following Information Request. Please request Cangene to respond by 30 April, 2014.

1. With regard to response to CR item 4, you have provided Table 17 which lists several of the analytical methods for in-process monitoring. This table does not contain other analytical methods which are used for in-process testing and are described in Section 3.2.S.4.1 of your application. Please list in a revised Table 17 all of the analytical methods employed for in-process testing, including, but not limited to that for (b) (4) .
2. With regard to the in-process controls for the (b) (4) , we requested in item 5a of the CR letter, that you express the Acceptance Limits for the (b) (4) , (b) (4) In your response dated 28 January, 2014, you included the (b) (4) , but did not express the data in (b) (4) . Please submit the data in (b) (4)
   With regard to the in-process controls for the (b) (4) process steps (CR letter, item 5a), we requested that you (b) (4)
   Your response to this item, dated 28 January, 2014, does not include the (b) (4) . Please submit the data in (b) (4)
   (b) (4)
   .
3. (b) (4) , however, should be controlled by (b) (4) , and the manufacturing process narrative should also include the activity units by which final product vials are filled. With regard to the in-process controls for the (b) (4) , we requested in item 5c of the CR letter that you provide the (b) (4) (supported by the process validation study). You provided information about th (b) (4) based on study F90-CR-030, but you did not support the (b) (4) information with a process validation study. Please include in your response the validation study for the (b) (4) .