DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: 04/28/ 2014

BLA 125426/0

Applicant: Emergent BioSolutions, MB, Canada (formerly Cangene Corporation),
US License# 1201 (Cangene Co. in Canada)
Registration (FEI) Number: 3003153579 (Cangene Co. in Canada)

Product: Recombinant Coagulation Factor IX (IB1001/ IXINITY) Recombinant – administered intravenously for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B.
- Each lyophilized vial contains nominally 500, 1000 or 1500 IU of Recombinant Coagulation Factor IX (DP).
-IB1001 DP is formulated in 5 mL of 10 mM histidine, 3% mannitol, 1% trehalose, 66mM NaCl, 0.0075% polysorbate 80, (b) (4)

From: Rabia Ballica, PhD, CBER/OCBQ/DMPQ/BI, HFM-675

Lead office: OBRR

Through: Carolyn Renshaw, Branch Chief/MBR1/DMPQ/OCBQ/HFM-675

Subject: Mid-Cycle Review Memo for the Biologics License Application (BLA) re-submitted- electronically January 27th, 2014 in response to the February 1st 2013 Complete Response (CR) letter.
-Original BLA submission received April 6th, 2012 (submitted by Inspiration Biopharmaceuticals)
-FDA CR letter issued February 1st, 2013
-Firm's Complete Response to February 1st CR letter - received January 27th, 2014 submitted by Cangene Corporation in Manitoba, Canada

Purpose of submission: Resubmission of Biologics License Application for IXINITY™ (IBl00l) as a complete response submission in response to FDA Complete Review letter of BLA STN 125426/0)

Deficiencies and Information Request:

The firm's response to the items (23-25) of the February 1st action letter issued in 2013 and the January 27th 2014 submission have been reviewed and the following deficiencies have been found (*refer to Appendix section of this memo p.8-p.20 for details of review*). The firm needs to address the deficiencies by May 20th, 2014.

1) Regarding (b) (4) testing at (b) (4) :

• We have reviewed your response to the item 24a of the February 1st action letter issued in 2013. It is unclear from your response what (b) (4) limit you use for test results to determine if the (b) (4) testing is "passed or failed". Please comment and indicate the limit for pass/fail.

• In the January 27th, 2014 submission, on page 4 of Section "3.2.P.3.3 Manufacturing Process and Process Controls" (manuf-process-and-controls.pdf), you state that (b) (4) testing has been removed from commercial specifications. Please provide justification for removing the (b) (4) testing from commercial specifications.

2) Regarding (b) (4) test method validation at (b) (4) :

You indicate in your response to our complete response item 25 that the validation of the integrity testing (b) (4) will be completed in early 2014. Please provide results of this validation along with the associated validation protocol in an amendment to the file if available. If not available at this time, please provide a request to submit this information as a post-marketing commitment (PMC) submission final study report. Please provide your PMC submission date**.**

3) We note that Batch Record (b) (4) is provided in the January 27th 2014 submission for a DS lot manufactured with the modified process, but there is no batch record submitted for DP lot manufactured from this post-change DS lot (DP Lot# (b) (4)). Please submit the batch record for DP lo (b) (4) along with a summary of deviations occurred during this DP lot manufacturing.

SUMMARY

Purpose of the January 27th 2014 Submission and History of the Bilological Licence Application:

The original BLA for Recombinant Coagulation Factor IX was submitted April 12, 2012 by Inspiration Biopharmaceuticals. Because of the major manufacturing and clinical issues (*refer to the review memos uploaded in EDR before February, 2013*), a complete response letter was issued February 1, 2013. Later in 2013, this product was acquired by Cangene Corporation.

Cangene Corporation responded January 27th, 2014 (re-submission) to the deficiencies outlined in the February 01, 2013 action letter for the BLA. As a result, sections of the BLA have been revised to include new information related to this complete response. A summary document highlighting the major changes to the BLA has been prepared and included with this re-submission. Cangene Corporation notified FDA March 6th, 2014 stating that Cangene Corporation started doing business under the trade name "Emergent BioSolutions" as of February 21, 2014 (the effective date).

Product and Indication:

IB1001 (proposed brand name, IXINITY™), Coagulation Factor IX (recombinant), is a sterile, nonpyrogenic lyophilized white to off-white powder, provided in a single-use glass vial contained in a kit with Sterile Water for Injection (WFI) and/or ancillaries (vial adapter with filter and infusion set which are CDRH approved Class II devices). The product is contained in a (b) (4) glass vial (10 mL) with a (b) (4) chlorobutyl rubber stopper (20 mm), aluminum seal and a plastic flip-off cap. Each single-use vial contains nominally 500, 1000 or 1500 international units (IU) of coagulation factor IX (recombinant). The final product is formulated in 5 mL of 10 mM histidine, 3% mannitol, 1% trehalose, 66 mM NaCl, 0.0075% polysorbate 80, (b) (4) and contains no preservatives. The accompanying diluent for reconstitution of one vial of IXINITY is 5 mL of sterile WFI (manufactured at (b) (4)) provided in a pre-filled 10 mL (b) (4) glass Syringe. All three dosage strengths yield a clear, colorless solution that is free of visible particles upon reconstitution. Recombinant Coagulation Factor IX (approximately 55,000 daltons) is administered intravenously and intended for control and prevention of bleeding episodes and peri-operative management in patients (in adults and children ≥ 12 years of age) with hemophilia B.

Description of Manufacturing Process and Changes:

Drug substance (DS) is manufactured at (b) (4) (*2.3.S.2 Manufacture*). Pre-approval inspection of this contract manufacturing site will be conducted (b) (4) There are changes to the DS manufacturing as summarized below:

(b) (4)

(b) (4)

Review of other changes/adjustments to the limits/acceptance criteria (in general tightened based on process capability/historical data) is deferred to the product reviewer. In addition to the adjustments to in process limits, the viral filtration step has been re-validated (*VAL-30187-02*) and HCP assay has been modified. Evaluation of these modifications is also deferred to the product office reviewers.

There are no changes to the drug product (DP) manufacturing at (b) (4), except for reconstitution time. The firm has tightened reconstitution time from (b) (4) based on process capability, and its assessment is deferred to the product reviewer. The manufacturing process for DP starts with (b) (4) and filled into vials. The vials are partially stoppered and transferred to a lyophilizer. The solution is lyophilized, and the vials are stoppered and sealed. A final DP solution at a weight up to approximately (b) (4)) is used for filling to achieve the maximum lyophilized DP lot size of (b) (4)

Inspection of the (b) (4) DP manufacturing site will be waived because of its inspection history (*refer to the table in next section of this memo*) and successful pre- and post-change conformance runs (*refer to the pertinent section of this memo and 2013 DMPQ review memo - uploaded in EDR*).

Manufacturers and Testing Facilities:

Manufacturer/Testing Facility	FEI #	Inspection History	Responsibilities
(b) (4)			
Cangene BioPharma* *1111 S. Paca Street* ***Baltimore, MD 21230 USA*	1000512361	-Inspection 03/31-04/09/2014 by BLT-DO **VAI,** 483 issued	* In 3.2.P.3.1 Manufacturers of the complete response submission: "Drug product labeling, packaging (vials and kits) and storage" indicated
(b) (4)			

Cangene Corporation ***155 Innovation Drive*** ***Winnipeg, MB R3T 5Y3 Canada***	**3003153579**	**-Inspection 06/12-06/21/2012 by CBER** **VAI, 483 issued**	-Drug product release testing: polysorbate 80, mannitol and trehalose -Drug product release - Release of drug substance for drug product manufacturing
(b) (4)			

NAI: No action indicated
VAI: Voluntary action indicated
CI: Corrective action indicated

There are changes to testing sites. (b) (4) will be responsible for all release and stability testing (used to be only for stability testing). Excipient testing, which was to be performed at (b) (4), will now be performed at Cangene (Winnipeg, Manitoba).

Process Validation and Equipment Qualification:

Process validation (PV) runs were executed using the post-change manufacturing process (with added (b) (4) step) (*3.2.S.2.5 Process Validation and/or Evaluation*). **Conformance DS batches** (b) (4) were produced after the facility enhancements and after the inclusion of the (b) (4) step for increased HCP clearance. There were no critical deviations that occurred during the production of the three DS lots (upstream and downstream). VAL-30156-12 covers the upstream manufacturing process, documenting the parameters selected for trending and verification of the process step performance. VAL-90012-06 documents the three consecutive downstream at-scale lots used for the conformance campaign after both the facility improvements and after inclusion of the (b) (4) step. Data from this report is identified as "Post-(b) (4) data". Results from the upstream and downstream DS lots met the acceptance criteria for the attributes evaluated. (b) (4) limits were met.

Results (*summarized in Section 3.2.P.5.4 Batch Analysis*) from DP PV runs (**conformance DP lots**(b) (4) met in process and release specifications for all the quality attributes (e.g., appearance, particulates, endotoxin and sterility and so on).

Deviations were investigated and CAPA were implemented where needed. Deviations occurred during DS manufacturing will be followed up during the upcoming pre-approval inspection of (b) (4). IQ/OQ/PQ, cleaning procedures (along with sterilization procedures where applicable) for all the equipment used in DS manufacturing (including new (b) (4)) will be reviewed during the pre-approval inspection of (b) (4).

Batch Record (b) (4)) is provided in the January 27th 2014 submission for a DS lot manufactured with the modified process, but there is no batch record submitted for the DP lot manufacturing from this post-change DS lot (*refer to IR items*).

Stability:

Stability results are summarized in Section "*3.2.P.8.1 Stability Summary and Conclusion*" (*stability-summary.pdf*). Based on the available stability data, a shelf-life is proposed for the drug product of 24 months when stored up to 25°C.

Long term stability and accelerated studies for the DP lots made at (b) (4)) from IB1001 DS manufactured using the modified commercial process that includes the new (b) (4) in the final container are ongoing. Currently (b) (4) lots of DP manufactured using DS made by the modified process are on stability ((b) (4) (500 IU), (b) (4) (1000 IU) and (b) (4) (1500 IU)) (*as outlined in Table 1 through Table 3 of 3.2.P.8.1*).

Current Stability Protocol for Drug Product Lots Stored at 5 ± 3°C, 25 (b) (4) C and (b) (4) (Studies initiated 2012 onwards) include appearance/solubility time testing at the time points of month 0 (for all storage conditions), 1 (for all storage conditions), 2 (for only (b) (4) 3 (for all store conditions), 4 (for only (b) (4) 6(for all store conditions) , 9 (for 5 ± 3°C, 25 (b) (4) C), 12 (at 5 ± 3°C, 25 (b) (4) °C) , 18 (for 5 ± 3°C, 25 (b) (4) °C) , 24 (for 5 ± 3°C, 25 (b) (4) C) , 30 (25 (b) (4) °C),(b) (4) at month 0, month 6 (only for (b) (4) and sterility testing at month 0 for all the stability conditions and (b) (4) for both 5 ± 3°C and 25 (b) (4) C.

The firm states that all lots passed sterility test to date, but has not specified any lot numbers and time points (e.g., at release and/or expiry). It is likely that the firm has not had any sterility test result at expiry yet for the lots manufactured with the modified process (process with (b) (4)). In *Section "3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment"*, it is noted that Cangene commits to monitoring the stability of the on-going 500, 1000 and 1500 IU strength (b) (4) stability drug product lots (i.e. those made using DS that was manufactured before the new (b) (4) step was introduced) through at least (b) (4) . Cangene further commits to inform the authorities should any unexpected issues arise . In addition, Cangene commits post-approval to place at least (b) (4) IXINITY (b) (4) on the stability program annually following ICH recommended time points at both 5 ± 3°C and 25 (b) (4) C, rotating among different dose strengths. The firm reports that the stability lots manufactured pre-change met the specifications for appearance, sterility and particulates at the time points tested (*3.2.P.8.3 Stability Data – Low (500 IU), 3.2.P.8.3 Stability Data – Medium (1000 IU), 3.2.P.8.3 Stability Data – High (1500 IU)*). The evaluation of stability data is deferred to the product reviewer.

APPENDIX

Review of Action Items 23-25

Item 23

Regarding drug substance manufacturing at (b) (4):

a. An acceptable inspection of your drug substance contractor's facility in (b) (4), is required prior to licensure. This inspection could not be scheduled during your first cycle review due to proposed changes in your process.

b. Manufacturing information was provided for (b) (4) but only bulk release testing results are provided for (b) (4) and no information was provided for (b) (4). Please provide a manufacturing summary for (b) (4).

Cangene Response to Item 23a

The drug substance contractor's (b) (4) facility in (b) (4) is available for inspection prior to licensure.

Cangene Response to Item 23b

As discussed in Section 3.2.S.2.5, Process Performance Qualification (PPQ)/Conformance batches used in the former commercial process validation studies included (b) (4) lots, (b) (4) manufactured pre-facility improvements (b) (4); VAL-90012-02) and (b) (4) manufactured post-facility improvements ((b) VAL-90012-05). Lots manufactured following the initial conformance (i.e. (b) (4)) **were not considered validation lots**, but data summarizing the in-process results are provided in ***VAL-90012-04*** (b) (4) were released for use in clinical studies; however, (b) (4) was not released due to an operator error that caused a critical deviation at the (b) (4) step.

Following implementation of an additional (b) (4) to ensure adequate removal of host cell proteins (HCP), PPQ was executed as Conformance Campaign 3, documented under *VAL-90012-06*. The IB1001 DS manufacturing process with the (b) (4) step was validated and reduces HCP levels to less than or equal to (b) (4) Chinese Hamster Ovary protein (CHOP) equivalents per mg of protein as measured by a (b) (4) assay (b) (4) Section 3.2.S.4.3). A risk assessment determined that there was no impact to the previous process steps with the inclusion of the (b) (4) step as there were no changes to any of the upstream operations after completion of the PPQs without the downstream (b) (4) step. The validation of the upstream process is therefore documented under the reports for the first two

PPQs. The valid manufacture of the upstream material for the downstream conformance runs with the (b) (4) was documented under the existing Continued Process Verification protocol (*VAL-30156-12*).

Reviewer's comment: *Acceptable*

VAL-90012-04 *(process-validation-5.pdf) does not refer to/identify explicitly* (b) (4) *lots (no lot numbers matching* (b) (4) *). Different lot numbers (e.g., downstream lots* (b) (4) *) other than* (b) (4) *are indicated in this document as listed below. However, based on the review of other sections of the January 27th submission, DS lots (downstream lots) indicated in this report corresponds to* (b) (4) *. These DS GMP runs were executed prior to the DS manufacturing modification for additional* (b) (4) *step.*

VAL-30156-12 (control-critical-steps-3.pdf) "F90 Continued Process Verification Annual Summary Report", ***lots*** (b) (4) *summarizes manufacturing information for the lots manufactured with the modified process (in that a* (b) (4) *step is added). Associated lot numbers are identified in the table below*.

Table 1. List of F90 (b) (4) Batch ID and Lot Numbers included in this (b) (4) Assessment.

(b) (4)

Information on VAL-90012-06 is included in the Process validation section of this review memo.

Item 24

Regarding drug product manufacturing at (b) (4)

a. You state in Section 2.3.P.3 "Manufacture" of the original BLA submission (page 11) that (b) (4) testing is performed (b) (4) , but it is unclear whether this method is validated. Please provide validation summary (e.g., including a description of test parameters, test conditions, testing procedures, and acceptance criteria for parameters evaluated) and results (a summary of validation data) for the (b) (4) testing method.

b. The information provided in Section "Responses to Oct 11, 2012 Information Request"

of Amendment 9 in response to 4.5 Question 4d (regarding the (b) (4)) does not fully address the issue indicated in our question (4.5 Question 4d in Amendment 9). Your response only describes the (b) (4)

c. Your temperature mapping study at (b) (4) (included in Section 3.2.P.2 Pharmaceutical Development) that supports the development of the lyophilization cycle does not include clear information on where thermocouples are placed on shelves and the correlation between product and shelf temperatures. Please indicate locations of the thermocouples per shelf and shelves used for the temperature mapping study and collapse temperature of the product and discuss any warm and cold spots identified, consistency of temperature readings and the relation between the product and shelf temperatures.

Cangene Response to Item 24a

(b) (4)

n • (b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4) [redacted]

Reviewer's comment: *Information on IQ/OQ of the* (b) (4) *is provided*, but *the provided information in the response is not complete. Important information in the response above is highlighted in bold and underlined.*

(b) (4) [redacted]

IR comments:

- *We have reviewed your response to the CR item 24c. It is unclear from your response what* (b) (4) *limit you use for results to say "passed or failed". Please comment and indicate the limit for pass/fail.*

- *In the January 27th, 2014 submission, on page 4 of Section "3.2.P.3.3 Manufacturing Process and Process Controls" (manuf-process-and-controls.pdf), you state that* (b) (4) *testing has been removed from commercial specifications. Please provide justification for removing* (b) (4) *testing.*

- *Please also verify that you will be using your validated* (b) (4) *testing method to assure the integrity of the drug product container closure (CC) system (this will not be verified at this time and depends on the firm's response to the question above).*

According to the information contained in my 2013 review memo- uploaded in EDR, the (b) (4) *testing was performed* [redacted] *In any case, the firm needs to provide a clear justification for their statement for removing the test.*

I also note from the information provided in 3.2.P.2 Pharmaceutical Development that the vials (b) (4) [redacted] *. It is also noted in Section 3.2.P.2. that his* (b) (4) *provides* (b) (4) [redacted] *to the vials. Based on this information, the firm needed to establish a limit for the* (b) (4) *inspection.*

(b) (4)
(b) (4)
[redacted]

Cangene Response to Item 24b

(b) (4)
[redacted]

(b) (4)

Reviewer's comment: *Acceptable. Important information in the response above is highlighted in bold and underlined.*

(b) (4)

Cangene Response to Item 24c

For transferring manufacturing of Drug Product (DP) to (b) (4) Site, the lyophilization parameters were identical to those developed by (b) (4) In this case, verifying only (b) (4) was deemed necessary on **the laboratory scale lyophilizer**. This was performed by (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Item 25

Regarding diluent manufacturing at (b) (4)
You state in Amendment 9 that the (b) (4) diluent syringes will be tested for integrity at specified time points. You have also included a description of integrity testing (b) (4) you plan to perform, but it is unclear whether it is validated. Please provide validation summary and results for the integrity test method you described in Amendment 9.

Cangene Response to Item 25
(b) (4) testing has been completed as part of the container-closure integrity evaluation. Results for sterilized diluent syringes batches (b) (4) passed at the 9 month test time point, and for batch (b) (4), at the 3 month point, as referenced in Amendment 9 to the BLA (Sequence 0009: response-oct11-info-request). The testing was performed based on a method derived from a validated (b) (4) test.

In support of container and closure integrity is the fact that media fills are performed with this specific container and closure on a periodic basis as part of aseptic processing validation. No integrity issues have been observed.

Another batch of sterilized diluent syringes will be manufactured in early 2014. **The validation of the integrity testing (b) (4) will be completed at that time**.

Reviewer's comment: *Not addressed*

The firm's response implies that the method without in house validation has been successfully implemented up to now and therefore there has been no need to validate the (b) (4) *method.*

The firm has not validated the (b) (4) *testing method yet, but the firm indicates that the validation will be conducted when another batch of sterilized diluent syringes are manufactured, in early 2014. Therefore, results of this planned validation needs to be provided in* ***a PMC.***

IR comment*:*
You indicate in your response to our complete response item 25 that the validation of the integrity testing (b) (4) *) will be completed in early 2014. Please provide results of this validation along with the associated validation protocol in an amendment to the file if available. If not available at this time, please submit the validation protocol and associated results in a post-marketing commitment (PMC) submission. Please provide your PMC submission date.*