**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**: July 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) – 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:** Final 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
-The product was acquired by Cangene Corporation as of February 15, 2013
-Firm's Complete Response to February 1st CR letter - received January 27th, 2014 submitted by Cangene Corporation in Manitoba, Canada
-Cangene Co. started doing business under the trade name "Emergent BioSolutions" as of February 21, 2014 (the effective date)

**Purpose of submission**: Resubmission of Biologics License Application for IXINITY™ (IBl00l) as a complete response submission in response to FDA's action (CR) letter for BLA STN 125426/0

## Recommendation

There are no outstanding review issues from DMPQ review standpoint based on the evaluation of the information provided in the January 27th 2014 re-submission of BLA and its amendments (*Amendments dated May 20th, June 3rd and June 27th, 2014*). Therefore, approval of BLA 125426/0 is recommended. However, deficiencies identified during the pre-approval inspection of (b) (4) have not been resolved and therefore a CR letter will be issued.

## SUMMARY

**Product and Indication**:

IB1001, recombinant Coagulation Factor IX (proposed brand name IXINITY™), 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). 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 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 (55,000 daltons) is administered intravenously and intended for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B (Control and prevention of bleeding episodes in adults and children ≥ 12 years of age with hemophilia B).

**Manufacturers**:

IB1001 drug substance is manufactured at (b) (4) . located in (b) (4) (*refer to 2.3.S.2 Manufacture of the BLA submission and DMPQ review memos dated April 28 2014 and January 18th 2013*). Pre-approval inspection of this contract manufacturing site was inspected (b) (4) . A 15-item FDA Form 483 was issued by the inspection team to (b) (4) senior management on (b) (4) . The firm submitted responses to this 483 June 17, 2014. Based on the assessment of the (b) (4) responses by the inspection team, approval of (b) (4) manufacturing site in (b) (4) for manufacturing of the drug substance cannot be recommended at this time because of the outstanding product related inspectional issues such as issues with (b) (4) responses to FDA Form 483 Items 1, 2 and 5 (*refer to July 14th assessment memo for 483 responses*).

IB1001 drug product is manufactured at a contract manufacturing site, (b) (4) (*refer to DMPQ review memos dated April 28 2014 and January 18th 2013*). The pre-approval inspection of (b) (4) contract manufacturing site ((b) (4) ) for manufacturing of the drug product has been waived based on criteria outlined in CBER SOPP

8410 "Determining When Pre-Licensing/Pre-Approval Inspections are Necessary" (*for details, refer to July 9th wavier memo*).

Sterile water for injection (WFI) as a diluent for the reconstitution of Recombinant Coagulation Factor IX is manufactured at the (b) (4) contract manufacturing site ((b) (4) Contract Manufacturing, (b) (4) - located in (b) (4) . The pre-approval inspection of (b) (4) manufacturing site (b) (4) has been waived based on criteria outlined in CBER SOPP 8410 (*for details, refer to July 9 wavier memo*).

(b) (4) ) located in (b) (4) performs release and stability testing of IB1001 (b) (4) drug product, but did not have any inspection history with FDA. Therefore, the inspection of this testing facility by ORA (b) (4) ) was requested. ORA performed this inspection in (b) (4) ). No FDA 483 form was issued. This inspection is classified as NAI (no action indicated).

**Submission Review:**

The original Biologics License Application (BLA) was submitted April 6, 2012 by Inspiration Biopharmaceuticals. This original BLA submission was reviewed (*refer to January 18th 2013 DMPQ review memo and product office review memos*) and major deficiencies were found. A complete response (CR)/action letter was issued February 1st, 2013. Later in 2013, recombinant Coagulation Factor IX was acquired by Cangene Corporation (as of February 15, 2013). Cangene Co. responded to the February 1st CR items January 27th, 2014. Cangene's responses to the DMPQ CR items 23-25 of the February 1st action letter were reviewed (*refer to DMPQ review memo dated April 28th 2014*). Because the firm's January 27th response did not address the CR item 25 adequately (*refer to DMPQ mid-cycle review memo dated April 28, 2014*), information on validation of the diluent container closure integrity test (CCIT) method (b) (4) ) was requested April 28th (*refer to the IR e-mail uploaded in EDR*). This information request (IR) was discussed through May 1st and May 29th teleconferences and associated e-mails (*refer to the teleconference minutes uploaded in EDR*) before June 27th amendment submission. Validation protocol and results for the CCIT method validation was submitted in June 27th amendment. Based on the information provided in the diluent container closure related sections of the January 27th re-submitted BLA and its amendments (*May 20th, June 3rd and June 27th*), the CCIT method ((b) (4) method) validation (that is submitted with June 27th amendment) is acceptable.

In summary, there are no outstanding review issues from DMPQ review standpoint and therefore approval of this BLA is recommended. However, deficiencies identified during the pre-approval inspection of (b) (4) have not been resolved and therefore a CR letter will be issued.