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: February 24, 2015

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: Review memo for Amendment submitted January 15, 2015 in response to December 16, 2014 information request (IR)
Submission History:
-Original BLA submission received April 6th, 2012 (submitted by Inspiration Biopharmaceuticals)
--FDA CR letter issued February 1st, 2013
-BLA re-submitted- electronically January 27th, 2014 in response to the February 1st 2013 Complete Response (CR) letter by Cangene Corporation in Manitoba, Canada
-- FDA CR letter issued July 29th 2014
-Firm's complete response to the FDA's CR letter issued July 29th 2014 was received October 28, 2014

Purpose of submission: To provide missing information on newly added ancillary device and update associated information in Section 3.2.R

SUMMARY

The 2nd complete response (CR) letter for BLA 125426/0 was issued July 29, 2014. The firm responded to this CR letter with the October 28th 2014 submission. In this complete response submission, the firm reported a new ancillary device addition (a Class II device). The added device was sterile LUER-LOK™ syringe (administration syringe). Because information on this added device was not complete in the CR response submission (*3.2.R Regional Information*), December 16th information was requested. Response to the December 16th information request (IR) was received January 15th 2015. Summary of the information provided in those submissions is as follows:

Ancillary devices that come in contact with the reconstituted IXINITY are vial adapter with filter (*reviewed-refer to the January 18, 2013 review memo*), sterile LUER-LOK™ syringe (administration syringe) and infusion set (*reviewed-refer to the January 18, 2013 review memo*). Because there are no changes to the vial adapter with filter and infusion set, this memo will only cover evaluation of the proposed administration syringe information.

The administration syringe is a device used to draw reconstituted drug product from a vial, through a vial adapter, prior to connection to the infusion set (*3.2.R Regional Information*). This intended use is the same as the use indication approved by FDA/CDRH (*May, 2011*) according to the CDRH 510k clearance record for K110771. Note that the firm provided 510k number for the administration syringe upon request *(December 16th 2014*). I should also be noted that upon request, the firm provided product specification, representative certificate of conformity, drawing and product label for the syringe in the January 15th amendment. Sterilization via gamma radiation (10^{-6} SAL) is performed in accordance with (b)(4) guidelines. Biocompatibility is evaluated as outlined in ISO 10993 and pyrogenicity per (b)(4). No objectionable issues are noted. Evaluation of the compatibility of IXINITY drug product with the proposed administration syringe is deferred to the product reviewer.

AMENDMENT REVIEW

(*Amendment dated January 15, 2015*)

Please provide FDA 510(K) number, manufacturer, product specification and product label for the LUER-LOK Administration Syringe. Please also submit a representative certificate of conformity and a drawing of the LUER-LOK administration syringe if they are not contained in the product specification document of the syringe. For your response preparation, you may refer to Section 3.2.R of your original BLA submission (dated 03/30/2012) for this information request (e.g., refer to the information provided for vial adapter and infusion set in the original BLA submission).

Cangene Response to Item 1

In response to FDA's Information Request, **Module 3.2.R Regional** has been updated with

respect to the requested details around the LUER-LOK Administration Syringe. For ease of review, these details have been provided in Table 1 below.

Table 1 LUER-LOK Administration Syringe

Product Name	**Syringe, Piston**
Manufacturer	Becton Dickson and Company 1 Becton Drive, Franklin Lakes New Jersey
Manufacturer Catalog Number	Catalog No. 302830
FDA 510(K) Number	K110771
Product Specification	**admin-syringe-prod-spec**
Representative Certificate of Conformity	**admin-syringe-cert-conformity**
Product Label	**admin-syringe-product-label**
Biocompatibility Data	**admin-syringe-cert-conformity**
Drawing	**admin-syringe-diagram**

Reviewer Comment: Addressed

Product specification (*dated November 6, 2014*) for syringe 20cc BD-Luer Lok sterile summarizes the certificate for conformity to specifications and sterility. The certificate was reviewed by QA (*dated and signed by the firm*). The other information includes the following:
-BSE/TSE free
-302830 (manufacturer- Becton Dickinson)/BD302830 (supplier-(b)(4))

Representative certificate of compliance:
-In compliance with the current FDA quality system regulation 21CFR820
-Manufacturing sites registration per 21CFR807
-Production facilities in compliance with ISO 13485
-Sterilization via gamma radiation (10^{-6} SAL) in accordance with (b)(4) guidelines
-Biocompatibility in compliance with ISO 10993
-Pyrogenicity testing per (b)(4)

Product label: A copy of the label is provided

Drawing: Information on dimensions and a drawing of the syringe sold and marketed in the US are provided.

3.2.R. Regional Information
(*January 15, 2014 Amendment***)**

4. Ancillary Devices**

Ancillary devices that come in contact with the reconstituted IXINITY are the vial adapter with filter (*reviewed-refer to the January 1, 2013 review memo*), sterile LUER-LOK™ syringe (Administration Syringe) and infusion set (*reviewed-refer to the January 18 2013 review memo*).

***The firm describes the ancillary devices that are packaged with the drug product either in the single-pack, 8-pack or the drug product only presentations and are used for reconstitution and/or intravenous administration of the IB1001 (proprietary name: IXinity™) drug product (3.2.R in the original BLA submission).*

The firm has not indicated in the submission whether or not this is a convenience kit. According to FDA Draft Guidance 2015 "Guidance for industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products", this package fits the definitions for a co-packaged combination product (page 4) and convenience kit (page 11), because ancillary devices (21 CFR 820) are co-packaged with the drug product (21CFR 211). According to the information provided in the January 15th 2015 amendment, each of the ancillary devices:
- individually packed
- individually labeled by its manufacturer (label for each of the devices is provided in the submission)
- individually sterilized
-separately 510(k) cleared
-purchased separately by Cangene/Emergent
-no processing on individually packaged and labeled ancillary devices at Cangene/Emergent

4.2.2 Administration syringe

The Administration syringe is a device used to draw reconstituted drug product from a vial, through a vial adapter, prior to connection to the infusion set.

Table 5 LUER-LOK Administration Syringe Specifications

Attribute	**Specification**
Device Type	Syringe, Piston
FDA Regulation number	21 CFR 880.5860
FDA Product code	FMF
FDA Device class	2
FDA Regulatory Clearance	Must have a 510(K) clearance
Material	Syringe assembly consists of a plastic barrel with a graduated scale, a synthetic rubber stopper and a plastic plunger rod.
Connector Type	Male LUER-LOK
Quantity per pack	**Single, must be individually packed.**
Sterility*	**Sterile product, by either Ethylene Oxide or an Irradiation sterilization method.**
Biocompatibility	ISO 10993-1 for the intended use
Compatibility	Compatible with the diluent, vial adapter and drug product provided for the pack presentation

Refer to the statement under **f) on page 5 of this review memo: "**f)** The BD Single Use, Hypodermic Syringe and the predicate device are sterilized to **a SAL of 10^{-6} via an EtO or Irradiation sterilization process**" This statement is from the CDRH 510(k) clearance record for K110771 (dated May 13, 2011). Refer also the note above as** marked*

4.2.2.2 Product Compatibility

Evaluation of the compatibility of IXINITY drug product with the Administration Syringe is deferred to the product reviewer.

Reviewer's Comment: CDRH approval record for K110771 (*dated May 13, 2011*) was not provided in the submission, but found in the CDRH approval records. The following information is a summary of approved information. Note that the indicated use is the same as that is indicated in Section 3.2.R of BLA submission (*draw/aspiration of fluid*).

Highlights from the CDHR Clearance Record dated May 13, 2011 for K110771:

Trade Name: BD Single Use, Hypodermic Syringe
Common Name: Piston Syringe
Classification Name: Syringe, Piston
Classificiation: Class II, 21 CFR 880.5860

Device description: The modified BD Single Use, Hypodermic Syringe is a three-piece single use, hypodermic syringe with a 6% (Luer) connector in l ml Luer Slip, 3ml and 5ml Luer Lok and Luer Slip syringe sizes. The syringe assembly consists of a plastic barrel with a graduated scale, a synthetic rubber stopper, and a plastic plunger rod. The changes to the modified device from the predicate include a new synthetic stopper material and a new silicone based stopper

lubricant formulation. The syringe performance characteristics are equivalent to the predicate device. The BD Single Use, Hypodermic Syringe is intended for use by health care professionals for general purpose fluid aspiration/injection.

Indications for Use Statement
510 (k) Number (if known): **K110771**
Device Name: BD Single Use. Hypodermic Syringe
Indications for Use:
The BD Single Use, Hypodermic Syringe is intended for use **by health care professionals** for general purpose **fluid aspiration**/injection.

Technological Characteristics:
The principal device of this **5 10(k)** premarket notification is the result of a design change to the **predicate device (K980987)** conducted in accordance with Quality System Regulations, 21 CFR **820.** The BD Single Use, Hypodermic Syringe is Substantially Equivalent to the predicate device, given that:
a) The BD Single Use, Hypodermic Syringe has the same intended use as the predicate device
b) The BD Single Use, Hypodermic Syringe operates under the same operating principle as the predicate device
c) The BD Single Use, Hypodermic Syringe barrel and plunger rod use an identical design and identical materials as the predicate device
d) The BD Single Use, Hypodermic Syringe and the predicate device meet the requirements for manual use and use with power-driven pumps as defined **by ISO 7886-1** and ISO **7886-2** respectively.
e) The BD Single Use, Hypodermic Syringe and the predicate device component materials comply with **ISO 10993** as applicable to the intended use of the device
***f)** The BD Single Use, Hypodermic Syringe and the predicate device are sterilized to an **SAL of 10^{-6}** via an EtO or Irradiation sterilization process
g) The BD Single Use, Hypodermic Syringe is assembled and packaged at the same manufacturing location utilizing the same equipment as the predicate device
h) The BD Single Use, Hypodermic Syringe demonstrated equivalent performance to the predicate device during design verification testing.

Performance: Design Verification tests (functional, chemical testing/extractables, biocompatibility) were performed based on the risk analysis performed, and the results of these tests demonstrate that the BD Single Use, Hypodermic Syringe performed in an equivalent manner to the predicate device and is safe and effective when used as intended.