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 9, 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: Review Memo for the June 27th Amendment to the Biologics License Application (BLA), which was 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: To provide a complete test method validation report for the container closure integrity testing on the diluent pre-filled syringes in response to the April 28th information request

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Recommendation

Based on the information provided in the original BLA submission and its amendments (June 3rd and June 27th), validation of the container closure integrity test (CCIT) method ((b)(4) method) that is submitted with June 27th amendment is acceptable. The validated CCIT method, (b)(4) method, will be used by both Emergent Solutions and the diluent manufacturer, (b)(4), to evaluate integrity of the (b)(4) diluent pre-filled syringes. The (b)(4) method will also be used to support container closure integrity over the shelf life of the diluent (WFI).

SUMMARY

The firm submits this amendment in response to the April 28th information request. Because the firm's January 27th response did not address the complete response (CR) item 25 adequately (*refer to the DMPQ mid-cycle review memo uploaded in EDR*), information on the proposed container closure integrity test (CCIT) method ((b)(4)) validation 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 this June 27th amendment submission (number 34).

The (b)(4) method is referenced as a method for determination of container closure integrity (CCI) (*as described in* (b)(4)

The (b)(4) test (CCIT method) will be used for testing of the pre-filled syringes used for reconstitution of Emergent's IXINITY drug product (DP), which is a coagulation factor IX (recombinant) product. The CCIT method will also be used to support CCI over the shelf life of the diluent.

The single use 10 mL (b)(4) glass syringe delivers a nominal volume of 5 mL of Sterile WFI (SWFI) as diluent to reconstitute the lyophilized IXINITY DP for parenteral use (intravenous administration). The syringe consists of the glass barrel (b)(4), a sterilized bromobutyl stopper (plunger stopper) and a plastic rigid tip cap (PRTC) with a Luer-Lok adaptor as the primary packaging materials. The 10 mL (b)(4) glass syringes are received by the contract manufacturer (b)(4)

(b)(4) . The bromobutyl stoppers are also received from the supplier (b)(4) . The syringes are filled (b)(4) , Contract Manufacturing ((b)(4)), and shipped to (b)(4) to Emergent Baltimore for packaging.

The firm conducted a CCIT method validation on the (b)(4) 10 ml pre-filled syringes. Appropriate validation parameters, sampling plan and conditions were used in this validation and the validation was performed using appropriate positive (b)(4)) and negative ((b)(4)) controls and test articles from the manufactured diluent lots (*refer to sections of this review memo below*). Results met the acceptance criteria. (b)(4)

(b)(4) . Moreover, stability results from the diluent lots manufactured at (b)(4) met the acceptance criteria for sterility, endotoxin and other stability indicating parameters – evaluated at different time points such as month 0, 12, 24 (b)(4) (*for details, refer to June 3rd amendment to the BLA; amendment number 29*).

Of note, the (b)(4) method - validated with this amendment (June 27th amendment) by Emergent BioSolutions (BLA applicant) will be transferred to (b)(4) (contract manufacturer of the diluent) for the CCI testing on the (b)(4) prefilled syringes.

REVIEW

History of IR for CCIT on the Diluent Filled Syringes

The single use 10 mL (b)(4) glass syringe delivers a nominal volume of 5 mL of Sterile WFI (SWFI) as diluent to reconstitute the lyophilized IXINITY drug product (DP) for parenteral use (intravenous administration). The syringe consists of the glass barrel, a sterilized bromobutyl stopper and a plastic rigid tip cap (PRTC) with a Luer-Lok as the primary packaging materials. The 10 mL (b)(4) glass syringes are received by the contract manufacturer (b)(4) from the supplier (b)(4) . The bromobutyl stoppers are also received from the supplier (b)(4) . The syringes are filled (b)(4) , contract manufacturing ((b)(4)), and shipped to (b)(4) to

Emergent Baltimore for packaging. The syringe supplier ((b)(4)) conducts (b)(4) testing on syringes (as integrity design verification tests) before shipping to (b)(4) (*refer to the January 2013 review memo*). (b)(4) conducts stability studies on the manufactured diluent lots that are not shipped (*refer to the January 2013 review memo and June 3rd amendment to the BLA*).

CR Item 25 on the February 1st 2013 action letter

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

Because the response above did not address the issue and did not include any validation data (*refer to my mid-cycle review memo for details*), the following April 28th IR was made (*refer to the April 28th IR – uploaded in EDR*):

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.

Following the April 29th internal mid-cycle meeting for BLA125426, it became apparent that a PMC would not be an alternate option (in case of incomplete validation), because lack of the diluent CCIT validation implies a safety concern for the BLA approval. Therefore, the April 28th IR was discussed through the May 1st – May 29th teleconferences and associated e-mails (*refer to the teleconference minutes uploaded in EDR*) to get the CCIT method validation completed prior to the BLA action due date July 29th. Eventually, the firm decided to complete the validation through an expedited validation study (being conducted in house) and make available the validation report

along with its results to the BLA (*response-to-request-dated-april-28-2014.pdf, pharmaceutical-development-1.pdf and pharmaceutical-development-2.pdf contained in June 27th Amendment*). This validation study is submitted with this amendment June 27th (*number 34*). In addition, June 3rd amendment (*number 29*) was submitted in response to the May 27th e-mail questions (*refer to the May 27th-29th teleconference minutes uploaded in EDR*) and stability results were included in this amendment (*number 29*). Results from Lo (b)(4) (not shipped overseas to US) met the acceptance criteria for sterility and endotoxin (at month 0, 12 and 24 for 5 ± 3°C and at month 0, 12, 24 and (b)(4) for (b)(4) ., and at (b)(4)) as well as other stability parameters. Closure integrity testing ((b)(4) testing method) was performed at month 9 and at the end of the stability study (results indicated as "conforms"). Results from Lot (b)(4) and Lot (b)(4) (not shipped overseas to US) also met the acceptance criteria for all the stability indicating parameters. It should be noted that (b)(4) CCIT method was not validated. However, the validated method submitted with the June 27 amendment will be transferred to (b)(4) (*refer to the May 27th-29th teleconference minutes uploaded in EDR, in particular to May 29th teleconference and associated e-mails*)

CCIT Method Validation

Method validation protocol (MV_264_pro_v1 STM No.500059):
(*response-to-request-dated-april-28-2014.pdf, pharmaceutical-development-1.pdf*)

The validation protocol describes the procedures and criteria for validation of standard test method (STM) 500214, container closure integrity Test (CCIT) by (b)(4) . This method will be used to confirm the contain closure integrity (CCI) for the sterile diluent (Sterile Water for Injection; SWFI), contained as 5 mL in a 10 mL glass syringe, used for reconstitution of the IXINITY™ [coagulation factor IX (recombinant)] drug product (DP). The CCIT method will also be used to support CCI over the shelf life of the diluent.

It is noted from the information provided in the validation protocol that the firm utilized the information published in the following article to design the validation study for integrity testing of the (b)(4) prefilled syringes.

(b)(4)

(b)(4)

(b)(4)

9 page(s) determined to be not releasable: (b)(4)