CMC Reviewers' Report

ADD: 29 July 2014
RPM: Leigh Pracht
Application type and number: BLA STN 125426/0
Product Name: Coagulation Factor IX (Recombinant) - IXINITY™, formerly IB1001
Proposed indication: For control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B
Applicant: Emergent BioSolutions (formerly, Cangene)
Reviewers Names: Nobuko Katagiri, Chava Kimchi-Sarfaty
Discipline: CMC

a. Reviewer's assigned areas *not* completely reviewed to-date

The review of (b) (4) *studies and validation has been completed. The review of response to CR 1-15 has been completed.*

b. Outstanding Information Requests

Information Requests regarding (b) (4) *have been addressed completely, but a few other CMC issues are still pending a sponsor response. There does not appear to be any outstanding IRs that could be exceptionally prohibitive.*

c. Date reviewer will complete the primary discipline review, if not complete.

25 May, 2014.

d. Key findings and substantive issues with the information and data in the application.

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 CR letter on 28 January, 2014.*

e. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

There are no substantial issues which could prevent approval of this submission.

f. Plan for addressing issues and the reason for the suggested approach

The following IRs were sent to the sponsor; Emergent BioSolutions has yet to respond to:

1. (b) (4)

2. (b) (4)

4. 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 listing all of the analytical methods employed for in-process testing, including, but not limited to that for (b) (4)

5. 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). In your response dated 28 January, 2014, you included the (b) (4) (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)

6. (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 the (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)