M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Center for Biologics Evaluation and Research

To: Files of STN 125426/0 & Edward Thompson, RPM

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Through: Mark Weinstein, Associate Deputy Director, IOD/OBRR
Timothy Lee, Acting Chief, Laboratory of Hemostasis (LH), DHRR/OBRR

Subject: Review of CMC information in amendment 40 provided by Cangene (Sequence 0041; response to the to a Complete Response Letter issued on July 29, 2014) for Coagulation Factor IX (Recombinant) [IXINITY™, formerly IB1001]

I. Background and summary

IXINITY™, formerly IB1001 is a recombinant coagulation factor IX (rFIX) product intended for control and prevention of bleeding episodes and peri-operative management in patients with hemophilia B.

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 (DS). 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 first clinical hold on 5 July, 2013, and responded to the CR letter on 28 January, 2014. This memorandum summarizes the review of the CMC information provided in amendment 35, with specific regard to the CR of 1 February 2013, items 10-16.

On 6 March, 2014 Cangene informed the Agency that Cangene is now a wholly-owned subsidiary of Cangene. Cangene updated the Agency on 21 November, 2014 stating that they will continue to operate as Cangene Corporation doing business as Cangene for the foreseeable future, and they do not anticipate any changes to the establishment name until sometime after the rFIX BLA PDUFA action date of 29 April, 2015. Therefore, Cangene will be the name that is used in association with this application.

Cangene's incomplete response to the FDA Form 483 regarding the observations cited during the (b) (4) inspection of (b) (4), their incomplete response to Information Requests sent on 7 April 2014

and on 21 April 2014, and additional deficiencies noted by other disciplines led to the issuance of a Complete Response (CR) Letter on 29 July 2014.

This review memo covers the CMC information in Cangene's response submitted on 28 October, 2014 to the CR on letter issued on 29 July 2014.

II. Review

Complete Review Question 1

With regard to the (b) (4) in the manufacture of recombinant Coagulation Factor IX (rFIX or F90), FDA has following comments:

(b) (4)

(b) (4)

c. Please provide the reports on complete characterization of three consecutive lots of rFIX (b) (4) Drug Product (DP) manufactured since June 2014.

d. Please submit the data from the comparison of manufacturing-scale and benchscale (b) (4) campaigns using the last three (b) (4) lots that were tested in your facility. The data should include, but not be limited to, (b) (4) .

Cangene response to Item 1a

The data will be reviewed by Hyesuk Kong from the Division of Biological Standards and Quality Control (DBSQC).

Cangene's response to Item 1b

Cangene's response to Item 1b is listed in Appendix 1 of the amendment.

The characterization of (b) (4) DP lots (Tables 1 and 2) detailed in this section pertains to the lots that (b) (4) (Table 1 copied from the Appendix).

Cangene provided partial raw data of (b) (4) DP tests in this appendix and further statistical analysis of the data comparing the affected lots to historical data.

Chunrong Cheng, OBE, statistician, provided the following comments on Cangene's statistical tools and the results:

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

The list of (b) (4) DP that (b) (4) is complete. However, is it not clear whether (b) (4) was filled into DP because no DP lots are listed in conjunction with this DS lot.

The raw data presented in the last 50 pages of the appendix do not include the lots that (b) (4) . Cangene did not comment on the reason why these lots were omitted from the raw data tables. Based on the statistician's comments, Cangene should explain the rationale for choosing the equivalence acceptance criteria (EAC) and provide statistical validation.

Cangene's response to Item 1c

Cangene's response to Item 1c is listed in Appendix 2 of the amendment.
The (b) (4) lots manufactured since June 2014 is detailed in this section.

Reviewers' comments

The raw data provided for the (b) (4) batches manufactured since June 2014 (b) (4) are complete and satisfactory. No special trends can be seen in these lots vs. previously historic data.
The use of EAC should be explained for all the analysis provided in response to Item #1.

Cangene's response to Item 1d

Cangene's response to Item 1d is listed in Appendix 3 of the amendment.
The characterizations of (b) (4) lots vs. bench scale characterizations are detailed in this section. Bench scale lots are characterized using the following attributes:

(b) (4)

No DP characterization is provided.
The following (b) (4) lots that are used for DS were tested in bench scale:

- (b) (4)

Bench scale results were provided for (b) (4) lots respectively.

Reviewers' comments

Bench scale results are provided for (b) (4) lots for (b) (4) (b) (4) lots, although Cangene committed to have (b) bench scale lots tested for each (b) (4) lot.
The results provided for these lots are satisfactory and are consistent with the large GMP lots and with the DS acceptance criteria.

Complete review question 2

In your response to item #l d in the CR Letter, dated January 28, 2014 and Information Request (IR) dated June 6, 2014 (STN 125426/0031), you submitted results of (b) (4) on three former process lots (b) (4) and three modified process lots (b) (4) after the implementation of several improvements to the (b) (4) method, such as (b) (4)

(b) (4)

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Cangene's response to item 2

Cangene provided new (b) (4) analysis of (b) (4) samples originated by (b) (4) . The report was prepared on 29 September, 2014.

The analyzed lots are listed in the following table copied from the (b) (4) report (b) (4)

(b) (4)

Reviewers' comments

The (b) (4) results are satisfactory and the response is complete.

Complete review question 3

In your response to CR item #4, you proposed new limits for (b) (4) . However, you have not completed the validation of the (b) (4) Please submit the validation data.

Cangene's response to item 3

The (b) (4) limit of (b) (4) was established through review of data from (b) (4) commercial manufacturing scale batches.

Reviewers' comments

The response is complete.

Complete review question 4

Regarding process-related impurities, please provide the following:

a. Results validating the removal of (b) (4) Chinese Hamster Ovary Host Cell Protein (CHO HCP), (b) (4)

b. Acceptance limits to the DP specifications for (b) (4) because you stated in your response to CR item # 12c, dated 28 January, 2014, that (b) (4) not tested for (b) (4), and there are no DP specifications in place for (b) (4) (section 3.2.P.5.1).

Cangene's response to item 4

Cangene had responded partially to this review question in amendment 35 and we found the data submitted regarding removal of (b) (4) satisfactory. At that point the spiking test results for the Chinese Hamster Ovary Host Cell Protein (CHO HCP) at the laboratory-scale were not provided.

Here, Cangene provided clearance data about Chinese Hamster Ovary Host Cell Protein from three manufacturing scale runs for (b) (4) steps and the (b) (4) Determination of HCP level is currently performed for (b) (4) with a criterion of (b) (4)

Previous results that were submitted to the Agency showed that clearance of CHO HCP in (b) (4) ranged between (b) (4) For (b) (4) earlier lots Cangene estimated that HCP concentration ranged between (b) (4)
(b) (4)

Reviewers' comments:

(b) (4) . Cangene should explain the rationale of testing (b) (4) in routine manufacturing.

We are concerned about the consistency of the HCP clearance: earlier results showed better clearance (b) (4) than the recent results reported in the response to the CR letter (b) (4) Therefore, more information should be provided regarding HCP clearance of lots GMP (b) (4) through the GMP that is currently manufactured to examine if HCP clearance is consistent.

Cangene also should clarify if they are using the same HCP assay in their spiked studies that they are using for their commercial lot testing.

Cangene has used two different units in their description of HCP clearance and it's not clear how mg/mL converts to ng/mg.

Complete review question 5

In your response to CR items #12 and #14, you described changes in data processing procedures, and reported that the potency test analyzer for (b) (4) was changed. Please clarify if the change also applies to DP. In addition, please provide data to compare the potency values determined using the (b) (4)

Cangene's response to item 5 and reviewers' comment
Cangene response and the reviewers' recommendation to this item were provided in the review for Amendment #35. IR was sent to Cangene and their response is under review.

Complete review question 6
In Tables 67 and 78 in your response to CR items #12b and #14b, dated January 28, 2014, you provided the acceptance criteria and limits for the in-process control parameters for (b) (4) DP manufacture. However, the response is not complete and should be amended with the following information:

a. Per the Agency recommendation in the CR Letter and in the April 2014 IR, (b) (4) In addition, the Agency also recommended including the activity units by which the final product vials are filled in the manufacturing process narrative.
Please include (b) (4) and revise the process narrative accordingly.

b. The proposed acceptance criteria for (b) (4) in the Release and Stability Specifications of the DP are too broad, and not representative of the test results derived from (b) (4) lots. Moreover, the acceptance limit for (b) (4) is not aligned with that for potency (the acceptance limit for potency is (b) (4) of the upper limit, while that for (b) (4) of the upper limit).
Please revise the acceptance limits based on your manufacturing experience.

c. In the Release and Stability Specifications of the DP, the proposed acceptance criteria for the (b) (4), are too broad, and not representative of the test results derived from (b) (4) lots. Please revise the acceptance limits based on your manufacturing experience.

d. In your response to the April 2014 IR concerning CR item #5a, the term "FIX (b) (4) " is misleading since the (b) (4) method measures (b) (4) only, not (b) (4). Please revise accordingly.

Cangene's response to item 6
Cangene implemented a potency test for the (b) (4). Section 3.2.S.2.2 has been updated to include the activity units by which the final product vials are filled. Cangene committed to set a specification based on data generated from the (b) (4) lots that were tested.

Updated specifications for (b) (4) DP are listed in section 3.2.S.5.1 and 3.2.P.5.1 respectively.
DP (b) (4) specifications have been tightened as follows:

(b) (4)

The (b) (4) acceptance limits have been tightened as follows:

(b) (4)

Cangene's response to the April 21, 2014 IR#2 Item 2 has been updated as requested with respect to "FIX (b) (4) " terminology. In addition, Cangene has subsequently committed to using the (b) (4) as mentioned above and will set a specification based on data generated from the (b) (4) lots.

Cangene provided the (b) (4) test results for (b) (4) for (b) (4) (Table 22). Figures 5-10 provide the correlation between the (b) (4) for these lots. The Coefficient of Determination (R^2) ranged between (b) (4)

Reviewers' comment:
The response is complete.

III. Summary and recommendations

The following Information Requests should be conveyed to Cangene. A response is expected by December 21, 2014:

1. With regard to your response to Item #1 of the CR letter:
   I. In your response to CR Item #1 you have used a value which you termed equivalence acceptance criteria (EAC). Please explain the rationale to determine the exact value and provide validation.
   II. In your response to CR Item #1 you have provided selective raw data for some, but not all lots. Specifically, no raw data were provided for the lots that (b) (4) Please provide all of the data.
   III. Please clarify whether (b) (4) was filled into DP because in your response to CR item #1 no DP lots are listed in conjunction with this DS lot.
   IV. In your response to CR item 1d you have provided bench scale results for rFIX lots tested with various (b) (4) lots. The number of bench scale lots varies among the various tested (b) (4) lots. In one case less than (b) (4) bench scale lots were tested (b) (4) Please provide data for (b) (4) bench scale lots tested using (b) (4) lot and commit to test (b) (4) bench lots for each newly introduced (b) (4) lot.

2. In your response to CR item #4 you have provided information regarding Chinese Hamster Ovary Host Cell Protein clearance. More information and clarifications are needed as follows:
   I. The Agency is concerned about the consistency of the HCP clearance because earlier results showed better clearance than the results reported in the response to the CR letter (b) (4) respectively). Please provide HCP clearance results for all lots, from lot (b) (4) to the most currently manufactured (b) (4) lot.
   II. Please clarify if you are using the same HCP assay in the spiked studies that you used in the testing of commercial lots.
   III. According to your report the (b) (4) may reach (b) (4) Please explain then why the use o (b) (4) in the spiking study is the worst-case condition if you aim to examine the (b) (4) .
   IV. You have used two different units in the description of HCP clearance: it is not clear how mg/mL converts to to ng/mg.