DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our Reference: CRMTS #9527
BL 125426/0

TODAY'S DATE: September 18, 2014 **PAGES:** # 4

TO: Steve McGregor
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FROM: Edward Thompson
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SUBJECT: FDA Response to Cangene Corporation (Emergent BioSolutions) Questions

PRODUCT: Coagulation Factor IX (Recombinant)

Although we continue to reserve September 23, 2014, at 3:15 p.m. to 4:45 p.m. for a teleconference with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible so that we may clear the meeting time. These responses would then become the official FDA responses to your questions.

Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our pre-meeting (preliminary) responses, we may not be prepared to discuss and/or to reach agreement on such changes at the meeting although we will try to do so if possible.

Please include a reference to CRMTS #9527 in your future submissions related to the subject product.

Questions from Cangene Corporation:

Chemistry, Manufacturing and Controls (CMC):

Sponsor/Applicant Question 1:
Does the Agency agree that the (b) (4) *test method meets the* (b) (4) *requirements outlined in* (b) (4)

FDA Response to Question 1:
The Agency agrees that the (b) (4) test meets the (b) (4) requirements in (b) (4) .

Sponsor/Applicant Question 2:
Does the FDA agree that the successful completion of additional validation proposed to assess (b) (4) *to confirm LOD/lack of* (b) (4) *of the method will verify the method is suitable for multiple* (b) (4) *lots and support that* (b) (4) *is not a contributing factor in the investigation of* (b) (4)

FDA Response to Question 2:
The Agency agrees that the additional validation of the (b) (4) test performed to confirm LOD/(b) (4) in the different (b) (4) lots ([i.e., (b) (4) to show they are suitable for testing using Cangene's (b) (4) testing methods) would indicate (b) (4) is not a contributing factor in the investigation of (b) (4) .

Sponsor/Applicant Question 3:
Cangene will be providing the expanded characterization data as outlined in Table 6 for the (b) (4) *limit as outlined in Table 4 and available drug product lots. Does the Agency agree that the proposed characterization as outlined in Table 6 is adequate to address CRL Item 1b?*

FDA Response to Question 3:
The Agency agrees that the proposed characterization for the (b) (4) (as outlined in Table 4 of the meeting package) is adequate to address CRL Item 1b. The extent of the characterization is outlined in Table 6 of the meeting package.

Sponsor/Applicant Question 4:
Cangene proposes to provide characterization data from release testing (Table 6) of three consecutive batches of (b) (4) *manufactured since June 2014 and perform a statistical comparison to historical batches of* (b) (4) *to verify that post investigation batches are consistent with our validated process. Does the Agency agree that statistical comparison on* (b) (4) *alone is sufficient?*

FDA Response to Question 4:
Your proposal to provide characterization data from release testing of three consecutive batches of (b) (4) manufactured since June 2014 and perform a statistical comparison to historical batches of (b) (4) is acceptable.

Sponsor/Applicant Question 5:
Cangene believes that provision of the data as outlined in Table 8 and Table 9 provides meaningful comparison of the performance of different lots of (b) (4) *at the bench- and manufacturing-scales to address CRL Item 1d, does the Agency agree?*

FDA Response to Question 5:
Complete release testing results of three consecutive batches of (b) (4) manufactured since June 2014, together with the extensive characterization as listed in Table 6 of the meeting package, are sufficient to address CRL Item 1d.

Labeling:

Sponsor/Applicant Question 6:
Does the agency agree that this approach is acceptable to ensure that comprehensive and clear labeling has been reviewed and is available at time of approval?

FDA Response to Question 6:
The approach to labeling as proposed in Section 6.1.5 of the meeting package is not yet acceptable because of issues related to (a) the new proposed kit presentation and method for administration, and (b) the reporting of annualized bleeding rates in the prescribing information.

a) Section 6.1.5 in the meeting package describes a new kit presentation, method of administration, and associated administration instructions. Please provide a risk and hazard analysis so that we can determine if a human factors usability study is necessary for the new kit and method of administration.

b) The meeting package states that "The package insert for IXINITY will be updated to include data on the mean annualized bleeding rates." Please also remove the square-root transformed annualized bleeding rates (ABR) entirely from the prescribing information, although you may keep them in the final study report. Because the ABR are not normally distributed, please consider adding the median ABR (in original scale) in the text of Section 14 as the primary presentation of ABR. You may supplement the medians with original-scale means in the text.

Chemistry, Manufacturing and Controls (CMC) – Regulatory:

Sponsor/Applicant Question 7:
The deficiencies identified in CRL items #3–17 are (a) readily addressable and will not require the review of substantive documentation to address the concern, or (b) have been

previously provided to the agency. This combined with the clarifications obtained from the Type A meeting, will allow Cangene to submit a succinct complete response. Cangene are therefore requesting an expedited review of the forthcoming complete response. Does the Agency support this request?

FDA Response to Question 7:
There is insufficient information to answer this question. The determination about the type and length of review will be made upon review of the complete response package.

Concurrence Page

Application Number: CRMTS #9527
Other Reference Number: BL 125426/0

Letter Type: Meeting Response

History:		
	Drafted	Edward Thompson/ August 26/2014
	Revised	Chava Kimchi-Sarfaty/ September 10, 2014
	Revised	Tim Lee/ September 17, 2014
	Revised	Irwin Feuerstein/ September 11, 2014
	Reviewed	Nisha Jain/ 2014
	Revised	Hyesuk Kong/ September 12, 2014
	Reviewed	James Kenney/ September 17, 2014
	Reviewed	Farshid Mahmood/ September 2014
	Reviewed	Trevor Pendley/ September 18, 2014

Concurrence

OBRR
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