Informal Teleconference Summary

Application type and number:	BLA 125661.0
Product name:	JIVI (Recombinant B-domain deleted human coagulation factor VIII conjugated with polyethylene glycol (PEG) (BAY 94-9027))
Proposed Indication:	Control and prevention of bleeding episodes and for surgical & long-term prophylaxis in patients with hemophilia A
Applicant:	Bayer Healthcare, LLC
Meeting date & time:	March 8, 2018 [11:30AM – 12:00PM]
Committee Chair:	Zuben Sauna, PhD
RPM:	Candace Jarvis Kay Owosela
Purpose:	To discuss the impurity determination by (b) (4)

FDA Participants

Lokesh Bhattacharyya, PhD, OCBQ/DBSQC/LACBRP
Candace Jarvis, OTAT/DRPM
Daniel Lagasse, PhD, OTAT/DPPT/HB
Kay Owosela, MSc. OTAT/DRPM
Zuben Sauna, PhD, OTAT/DPPT/HB
Hsiaoling Wang, PhD, OCBQ/DBSQC/LACBRP

Bayer Participants

Jefferson Douglas, CMC
Michelle Meng, Regulatory
Lisa Regan, CMC
John Teare CMC
Megan Ward, Regulatory-CMC
Lidia Wojnowski, CMC
Quan Yuan, CMC

Discussion Summary

1. The SOP CBER lab followed for the test is the most recent version in amendment 13 (dated Dec. 28, 2017). That SOP uses a (b) (4) Polysorbate 80.

2. CBER indicated that they used the (b) (4) which has (b) (4)

(b) (4) was purchased new specifically for the test and cleaned as per manufacturer's (b) (4) instructions before using.

3. In the section 4 of the SOP, it states that (b) (4) . That was how CBER lab connected the (b) (4)

Action Items:

FDA

1) Clean the system as per the e-mail from Bayer's representative Michelle Meng (dated 6 March 2018)
2) Repeat procedure using a (b) (4) purchased by the CBER lab as well as a new (b) (4) provided by Bayer

Bayer

1) Send FDA new samples, control with established limits, and new (b) (4)
2) Investigate trace amounts and how Polysorbate 80 (b) (4) impacts assay outcome.

Notes:

The teleconference was requested by CBER because the CBER laboratory found failing results when the drug product, JIVI (STN: 125661), was analyzed in the laboratory by (b) (4) assay following the procedure provided by Bayer, Inc. as part of the BLA review of the product. Specifically, CBER found that it was unable to meet some of the assay validity criteria (b) (4) of the drug product failed meet the proposed BLA specification.

Bayer indicated that the (b) (4) system must be (b) (4) polysorbate 80 (b) (4) They have seen (b) (4) in the presence of polysorbate 80 in the (b) (4) but did not know the reason. The assay is so sensitive to polysorbate 80 that they have a dedicated (b) (4) system for this assay. CBER explained that it was not possible for the CBER testing laboratory to have an (b) (4) system dedicated for JIVI testing, or for that matter for testing of any specified product. However, the CBER laboratory has not used polysorbate 80 in (b) (4) used in the same system for more than a year. Therefore, CBER does not think that there is any concern regarding the presence of polysorbate 80 in the (b) (4), even in trace amount, and that cleaning up the system as described in the e-mail from Bayer for the potential presence of polysorbate 80 (b) (4) is not necessary. The (b) (4) was cleaned as per manufacturer's (b) (4) instructions prior to use.

Bayer also indicated that it was very difficult to find a (b) (4) for this assays, which is suitable to perform (b) (4) of proteins in the (b) (4) of JIVI. CBER expressed concern about the lack of (b) (4) but agreed on the problem of finding a (b) (4) suitable for (b) (4) of JIVI. However, CBER was aware of another alternate (b) (4) , which, in their experience worked well above for (b) (4) . CBER could suggest the (b) (4) at the request of Bayer. However, CBER pointed out that they did not have any experience with JIVI on the suggested (b) (4) . It will be up to Bayer to decide if they want to evaluate the suggested (b) (4) and use it going forward. Use of the CBER suggested (b) (4) is not a binding to Bayer. [The (b) (4) information was sent to Bayer in a separate communication.]

Since no root cause for obtaining failed results in the CBER laboratory was identified in the meeting, CBER agreed to retest the sample after cleaning the system as per the method provided in the e-mail from Bayer (dated 6 March 2018) and requested additional samples and control from the same lots from Bayer for testing. Bayer agreed, and also offered to send a (b) (4) , which they found suitable to use. CBER agreed to the request.

CBER also expressed concern about Bayer's finding that presence of trace amount of polysorbate 80 (b) (4) significantly, for which Bayer provided no explanation. CBER felt that it would be possible that the (b) (4) are present in the product but are (b) (4) under the assay conditions used by Bayer because (b) (4) However, in the presence of the trace amount of polysorbate 80, a (b) (4) . CBER requested Bayer to investigate this possibility, to which Bayer agreed. CBER also requested Bayer to provide an approximate timeline for concluding the investigation and submit a report for CBER review within two weeks from the date of this meeting.