

## RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA    Submission ID: STN 125582/0  
Office: OBRR  
Product: Coagulation Factor IX (Recombinant), Albumin Fusion Protein  
Applicant: CSL Behring Recombinant Facility AG (CSLB)

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Communication Category:    Advice

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Telecon Summary: Discussion on question # 6 in the October 16, 2015 Information Request

### **FDA Participants:**

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### **Non-FDA Participants:**

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### **Purpose of the Teleconference:**

On October 29, 2015, CSLB requested this teleconference to obtain FDA advice on CSLB's proposal to respond to FDA's Question 6 in the 16 October 2015 information request. CSLB provided pre-meeting background information presented below.

BACKGROUND INFORMATION:

Below is Question 6 from FDA's 10 October 2015 request for information and other background material for this telecon:

6. *With reference to amendment 128582/0.41 submitted on September 18, 2015, please address the following issue: The data presented appear to show that impurities in Polysorbate 80 (PS-80) (b) (4)*

*Based on the above, we consider the purity of PS-80 to be critical. Please revise the specification for PS-80 to ensure control for the unknown impurities with the (b) (4)*

*We recommend you to use (b) (4) of rFIX-FP by (b) (4) in the presence of PS-80 to qualify each batch of PS-80.*

The data presented in BLA 125582, sequence 0041 showed that the presence or absence of 'additional Polysorbate components' (b) (4) observed for rIX-FP manufactured by the pilot and commercial processes respectively.

The different sources of PS-80 used for each of the pilot and commercial processes (from different manufacturers) were considered a most-probable cause for these additional Polysorbate components. Variations in PS-80, as a function of manufacture, has been previously described (Borisov 2011 - Submitted in BLA 125582/seq 0041).

Evaluation of (b) (4) (b) (4) has shown that at each process scale a (b) (4) response is achieved (Figure 1, Figure 2). Further supporting the hypothesis that PS-80 is the most-probable cause for the source of the additional Polysorbate components is that a (b) (4) consistent with commercial-scale batches is observed when commercial scale (b) (4) is (b) (4) in the pilot scale facility (Figure 3).

**Figure 1:** (b) (4)

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

(b) (4)

(b) (4) is identified as a Critical Quality Attribute at (b) (4) stages (Report 01020031- section 3.2.S.2.6-4). The CQA assessment specifically focused on the (b) (4)

CSLB acknowledges differences in the (b) (4) observed across the two scales of manufacture. To date these changes have not been correlated to any impact on patient safety, clinical efficacy or product quality (at release and over shelf life) and therefore the observed (b) (4) have no observable effect on the (b) (4) content.

Per FDA's request, CSLB is actively investigating the (PS-80) raw material used for the production of rIX-FP with the goals of firstly, identifying the root cause (PS-80 component(s)) of the observed (b) (4), and secondly, develop methods to control the quality of PS-80. These investigations include but are not limited to (b) (4) testing of rIX-FP produced using alternate PS-80 suppliers, (b) (4)

In parallel to the root cause analysis and future development of a PS-80 control strategy, CSLB commits to the following activities:

(b) (4)

**Questions to FDA:**

1. Does the FDA agree that it would be appropriate to implement (b) (4) as a characterization test to show consistency of manufacture for next 20 rIX-FP (b) (4) batches produced?
2. Does FDA agree that the (b) (4) (b) (4) 20 (b) (4) PS-80 (b) (4)

END OF BACKGROUND MATERIAL

### Summary of Teleconference:

CSLB informed the Agency that the investigation of the effect of PS-80 on product quality is ongoing. At this time, CSLB believed that the differences between the pilot and commercial scale (b) (4) materials observed by the (b) (4) method are caused by unknown impurities in PS-80. CSLB requested FDA's agreement on its strategy to investigate the effect of PS-80 on the product, including both prospective and retrospective studies of (b) (4) batches.

CSLB proposed to test 20 batches of (b) (4) 17 of which have been tested to date. CSLB committed to provide (b) (4) data on the 17 batches during the current review cycle as an amendment to the BLA. (b) (4)

CSLB informed the Agency that the (b) (4) method had not been validated. CSLB also believes that formal analytical validation of the (b) (4) method is not possible due to the complexity of the technique. With regard to the use of an unvalidated (b) (4) method, FDA agreed to accept the (b) (4) data under the condition that CSLB will demonstrate the suitability of the (b) (4) method for the purpose of comparison of product batches.

FDA stated that CSLB's proposal is reasonable but not comprehensive enough. FDA noted the following issues need to be addressed:

1. The proposed testing of (b) (4) is not an optimal way to assess PS-80 purity and may be accepted only as a temporary measure. FDA requested CSLB to permanently amend the raw material specification for PS-80 to include testing of each lot of PS-80 on receipt before it is used in the manufacturing process. If CSLB decides to use (b) (4) as a method to assess PS-80 purity, the (b) (4) method will need to be validated.
2. While the data provided by CSLB point to impurities in PS-80 as the most likely cause for the differences observed by (b) (4) between the pilot and commercial

scale samples, other factors may still be involved, so the development of a method(s) to assess the purity of PS-80 is critical.

CSLB commented that sample preparation for the analysis of PS-80 (b) (4) is very laborious, and asked FDA if alternative methods may be used. FDA answered that the recommendation to use (b) (4) is based on the fact that the nature of the PS-80 impurities (b) (4) and that (b) (4) was shown to be sensitive to these PS-80 impurities.

CSLB informed FDA that the work on identifying the impurities is under way and an alternative method will likely be developed for testing the PS-80 raw material. FDA noted that while we are open to using an alternative method, its acceptance will be dependent on the data which CSLB provides.

FDA requested CSLB to commit to the following while an alternative method to assess PS-80 purity is still under development:

(b) (4)

[Redacted]

[Redacted]

CSLB agreed with the FDA.

**End**