

Memo - Addendum to CMC review - Corifact

To: File (STN 125385/0) & Nannette Cagungun, RPMB/DBA/OBRR

From: Ze Peng, LH/DH/OBRR

Through: Timothy Lee, Acting Chief, LH/DH/OBRR

Subject: Addendum to CMC review regarding the acceptance criterion for -----
----- (b)(4) ----- in the manufacture of Factor XIII
Concentrate (Human)

Background

Factor XIII Concentrate (Human) is a sterile, preservative-free, heat-treated, lyophilized plasma protein product manufactured in the CSL Behring facility located in Marburg, Germany.

The previous --(b)(4)-- acceptance criterion for the -----
----- (b)(4) ----- Since this limit did not reflect CSL Behring's manufacturing experience and process capabilities, CAPT Martha O'Lone from DMPQ brought up this issue to the sponsor in January 2011. CSL Behring responded in Amendment 8 by including a warning level of --- (b)(4) --- for this in-process control parameter.

However, the FDA considered the inclusion of a warning limit of --(b)(4)-- is insufficient to control the process and thus, the quality of this intermediate. FDA discussed this issue with CSL Behring in 2 teleconferences on 10 February 2011 and 11 February 2011. Please refer to the respective telecon minutes for details. In summary, FDA stated that:

- The acceptance criterion for ----- (b)(4) -----
----- should represent CSL Behring's manufacturing experiences.
- The acceptance criterion should be set based on statistical analysis of the testing results generated from the (b)(4) available Factor XIII Concentrate (Human) lots. FDA would accept a value of Mean + 3 SD.

Response from CSL Behring

CSL Behring submitted their response in Amendment 14 on 14 February 2011. In it, CSL Behring revised the acceptance criterion for the referenced ---(b)(4)--- level to ----(b)(4)----.

The calculation of the proposed acceptance criterion is based on the -----(b)(4)----- Factor XIII Concentrate (Human) batches as listed in the following table:

----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	----- (b)(4) -----	----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
		----- (b)(4) -----	(b)(4)
(b)(4)			(b)(4)
----- (b)(4) -----			(b)(4)
(b)(4)			(b)(4)
(b)(4)			(b)(4)

FDA Comment: Although the proposed value is still -----(b)(4)----- calculated from the ----(b)(4)----, it is more representative of CSL Behring's manufacturing experience, and much -----(b)(4)----- . CSL Behring's justification is that the sample size should be -----(b)(4)-----, for them to comfortably use Mean + 3 SD for this limit. We conferred with Dr. Epstein and he found the proposed revised limit to be acceptable.

Conclusion

The revised acceptance criterion for the -----(b)(4)----- at Step - (b)(4)- is more representative of CSL Behring's manufacturing experience on Factor XIII. With the concurrence of Dr. Jay Epstein that this response is acceptable, we recommend moving forward with the approval of this BLA.