From: Cagungun, Nannette
Sent: Thursday, January 05, 2017 2:22 PM
To: Michele.Walsh@cslbehring.com
Subject: CMC Information Request_Stat_C1INH/CSL830

Our Reference: BL 125606/0

Dear Ms. Walsh:

We are providing the following comments and request for additional information on your June 30, 2016, biologics license application for C1 Esterase Inhibitor Subcutaneous (Human):

1. Please submit the study that established the acceptance criteria for Berinert manufacturing process, Study# IR-617-001-01.

2. Please provide the investigational study IR-688-002-02 on impurity analysis of CSL830 1500 IU.

3. Please provide a summary of the (b) (4) data that characterized the (b) (4) in the typical b) (4) obtained for CSL830 1500 IU, and also a justification for how these results are applicable to CSL830 2000/3000 IU final product.

4. Please provide SOPs for b) (4)

5. In Study# IS-617-015, you indicated that (b) (4) could not be determined due to difficulties with the test kit. Please provide further explanation for why the method did not work. Additionally, please justify how the expectation ranges defined within the previous study would be valid for CSL830 2000/3000 IU final product.

6. Please clarify the rationale for not including (b) (4) as a final release specification for CSL830 2000/3000 IU.

7. For the analytical method Q-04-003 Practicability and organoleptic properties, the specification was determined based on manufacturing experiences. Please provide summary of historical data from product manufacturing including any deviations or out-of-specification results and investigation reports.

8. For Q-04-314 (b) (4), the method validation report appeared to be the same report based on validation protocol No. MVP-04-314-Q0617U-01 for Berinert products. Please provide any revalidation studies, and/or summaries of deviations or out-of-specification results and investigation reports if any since the approval of Berinert products.

9. For the Q-10-121 b) (4), the method validation report covered

products including Berinert, CSL830 1500 IU, and the current product CSL830 2000/3000 IU. Please provide summary of historical manufacturing data for Berinert products including any deviations or out-of-specification results and investigation reports for this assay.

10. For Q-16-004 (b) (4), please provide summary of historical manufacturing data for Berinert products using this assay, including any deviations, and/or out-of-specification results if there were any involving this assay.

11. Please clarify whether the submitted method validation reports for Q-16-399 Purity are applicable to the purity measurement of both Berinert and CSL830 2000/3000 IU, or submit any additional validation studies for this method if available.

12. For Stability Study# 689-002US, please submit the (b) (4) for the Purity test and the (b) (4) (b) (4) for the (b) (4) test performed on all (b) (4) final product lots for each time interval and storage condition tested.

13. Table 3.2.P.8.1-1 in the original submission (125606/0.0) describes storage conditions that differ from the conditions included in version 2 of the same table in Amendment 125606/0.7 submitted on October 28, 2016. Please clarify.

14. In Process Validation Report (b) (4) from Lot (b) (4) showed (b) (4) (Table 11 in Section 7.2). Please indicate whether this deviation was investigated and provide the investigation report if available.

15. Please provide an expected timeline for the submission of additional updated stability data from Study# 689-002US. Also, please provide a plan for how the stability of your product will be monitored post-approval.

16. Please provide a side-by-side comparison of all the critical and non-critical process parameters, in-process tests and acceptance criteria, and final release specifications for Berinert, CSLB830 1500 IU, and CSLB830 2000/3000 IU.

17. Please provide validation documentation supporting the hold time for the (b) (4) manufactured according to production procedure (b) (4).

18. Regarding the process parameter "(b) (4)", please provide the final report of the (b) (4) study that will be used to support the new (b) (4) for this step.

19. Please provide the following change control documents for review; PR#136281, PR160694, and PR#162637.

20. Please provide the following documents for review; FS-617-022 and 900806-1.

21. Please consider implementing upper and lower limits as well as an alert limit for the process parameter "(b) (4) Also, please clarify what actions are taken in the event of nanofilter malfunction or blocking during filtration, and whether these actions are described in relevant SOP(s) for the virus nanofiltration step.

22. Please provide the final release testing results for all the CSL830 1500 IU batches used in clinical studies.

23. Please provide a list of lots that would be available for FDA release testing. Please indicate whether there are lots identified as potential launch lots for the US market.

24. You proposed a shelf-life for CSL830 2000/3000 IU of 36 months at +30°C/(b) (4) . Please review all submitted labeling documentation to ensure that this shelf-life is correctly indicated.

Please submit the requested information as an amendment to the file by Thursday, January 19, 2017, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact me immediately so a new response date can be identified.

Sincerely,
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