

Dr. Post

CBER's review of BLA 125285 and Protein Science Corporation's response to CBER's July 30, 2009 Information Request is ongoing. During a September 24, 2009 BLA meeting with CBER, Protein Science Corporation (PSC) acknowledged the failure of its clinical lot consistency study of the A/Wisconsin H3 component of Flublok conducted as part of study PSC04. CBER therefore stresses the importance of process validation to assure manufacturing consistency of Flublok.

CBER has the following requests for additional information. Numbering below, except for “Additional Requests”, refers to that used in CBER’s July 30, 2009 CMC Information Request which follows the numbering used in PSC’s April 28, 2009 response to CBER’s August 29, 2008 Complete Response (CR) letter.

1a. Concerning process validation:

We do not consider your manufacturing process sufficiently validated for licensure. The following information is requested:

- C) d) ii. You have provided no documentation to support your claim that the Quality Unit knew of and approved the ----(b)(4)--- step associated with Process Validation Lot ---(b)(4)-- prior to its execution on May 4, 2009. Please clarify your response concerning this issue. In addition, if documentation is not available please describe corrective and preventative actions you will implement to correct this recurring deviation.

(b)(4)

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- C) f) ii. The purity attained by the end of (b)(4) is surprising low and yet (b)(4) purity meets specification of (b)(4). Please provide data to support consistent purification at the step(s) that increase product purity.
- C) h) v. Please provide your assay to quantify Tween 20, the associated validation report, and Tween 20 results to support validation of the --- (b)(4) ----- step.

Concerning the Interim H3 Process Validation Report:

At CBER's request, PSC submitted an interim 2009 validation report on 15 June, 2009. Please submit the final 2009 validation report which should include, but is not limited to, the following:

- Data to validate the bulk filtration step.
- ----- (b)(4) -----
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- The maximum hold time (shelf-life) for monovalent bulk drug substance and data from stability studies to support this time.
- The temperature parameters used for incubation during bioburden tests. If the excursion noted in deviation 09-023 was out of these limits, state why the temperature excursion was deemed to have minimal impact on the result.
- Data to support validation of (b)(4) step using a --- (b)(4) -- column.
- Data to support validation of H1 and B HA purification by (b)(4) column chromatography.

Regarding your response to comment 2 (Process Characterization):

2g. Concerning re-use of columns:

- A) Please adjust your linear flow rate parameters for the ---(b)(4)----- columns to include a lower limit based on process capabilities.
- C) Please clarify testing performed to confirm complete removal of column storage solution prior to use.

Regarding your response to comment 3 (Product Specifications):

3b. Concerning --(b)(4)--- necessary to maintain minimum potency from release throughout your proposed dating period, to ensure a minimum potency at expiry:

- A) We agree with ---(b)(4)--- as the minimum potency release specification. The maximum release potency of ---(b)(4)---- is also acceptable. We strongly encourage your commitment to optimize stability in terms of SRID potency to narrow the difference between minimum and maximum potency in each dose. Please note that any changes to your process, drug substance/product formulation or testing methods that may impact product quality must be submitted as a supplement to your license.

Regarding your response to comment 4 (Stability):

4d. Concerning stability of monovalent bulks:

- C) PSC considers lots with -----(b)(4)----- rare exceptions and that this would trigger an investigation. There is currently no written specification that would trigger an investigation for -----(b)(4)----- . Please include an upper limit of --(b)(4)-- for the drug substance ---(b)(4)--- specification and provide the protocol followed in the event of an OOS --- (b)(4)----- result.

Regarding your response to comment 5 (Adventitious Agent Testing):

5c.ii.

(b)(4)

Regarding your response to comment 10 (Assay Methods and Validations):

10a.i. Concerning Assessment of purity by ---(b)(4)-----:

When assessing protein purity, -----(b)(4)----- In your previous response, you stated that -----(b)(4)----- therefore purity analysis was accurate. Please provide ---(b)(4)----- and ---(b)(4)----- for -----(b)(4)----- samples (one lot each of H1, H3 and B HAs) --(b)(4)-- for purity analysis to support your statement.

10c. Concerning DNA quantitation SOP and validation:

- A) Please explain the discrepancy between DNA removal efficiency in Process Development and full scale manufacture.
- B) The SOP for DNA quantitation by --(b)(4)-- method is confusing. It specifies dilution of the sample to ----(b)(4)---. Unless your validation shows no impact of protein concentration on the assay, each assay should include controls that are spiked into the matrix containing product at similar protein concentration as the test sample. The assay should also include a control that contains DNA measured by an alternate method in the QC laboratory. In addition, please explain why ---(b)(4)----- was included in the test and its impact on LOD of the assay.
- C) Validation of your ---(b)(4)---- DNA assay is not complete. Please provide results to identify the limit of detection when protein is added to the controls at amounts similar to those present in ---(b)(4)----- and final formulation. Also spike different amounts of standard into a bulk preparation that has no DNA detectable to determine accuracy of your limit test. In addition, repeatability of your test should be demonstrated.

10e. Concerning ----(b)(4)-----:

We agree that quantitative analysis for ----(b)(4)----- is unnecessary; however, it should be listed as a potential impurity.

10f. Concerning Triton X-100, (b)(4) and Tween-20 quantitation:

We agree with the specification of -----(b)(4)----- you have set for monovalent bulk drug substance. Please set your specification for Triton X-100 based on results

Regarding your response to comment 11 (Formulation and Filling):

- In the strain change update amendment dated 09/18/2009, we note that the B/Brisbane/60/08 HA gene that you cloned into baculovirus -----

Please explain how the decision to accept the clone --(b)(4)-- complies with your cloning SOP and provide evidence that antigenic properties have not been compromised.
- We have reconsidered your proposed proprietary name, Flublok, in consultation with CBER's Advertising and Promotional Labeling Branch (APLB) and conclude that under 21 CFR Part 201 the proposed proprietary name FluBlok is acceptable.

However, we have concerns with the presentation of the “Flublok” logo on proposed carton and label containers. Specifically, we are concerned that the use of italicized text for “*flu*” and block letter with a capitalized “B” for “Blok” in ***flu*Blok** on proposed carton and container labeling is misleading and fanciful because it overstates the efficacy of the vaccine by emphasizing the suggestion that the “flu” virus will be “blocked” or prevented when there is no guarantee that 100% of vaccinees will be protected. We recommend that you revise your logo accordingly, and submit revised proposed carton and container labels for FDA consideration.

If you have any questions, please contact the Regulatory Project Managers, Katherine L. Matrakas or Timothy A. Fritz at 301-827-3070.