

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

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

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

- 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) -----
-----.
- 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 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

from the 2008 season (do not include 2007). We agree that the concentrations will be below 0.02% and would consider this a more appropriate specification based on your manufacturing capabilities.

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

11d. Concerning process validation:

We understand drug product filling validation will take place in the near future. Please note that data from two 100% fills are required prior to licensure. This data should be submitted when available. Please acknowledge.

11f. Concerning container closures:

- A) Microbial failure occurs in the leak rate region of $10^{-4.5}$ to 10^{-3} std cc/sec, which roughly corresponds to leak diameters ranging from 0.4 to 2 microns. It is not clear if your method can detect a critical leak in the range mention above. Please submit a plan for demonstrating that the sensitivity of your container closure integrity test method can achieve adequate levels of detection.

- B) Container closure integrity validation must be repeated with vials used in the shipping validation study and this data must be submitted to CBER for review or repeat container closure integrity testing to include dynamic conditions (i.e., exposure to differential pressures to simulate anticipated product processing or distribution conditions).

11g. Concerning information regarding ----(b)(4)----- Stoppers:

Please submit your test plan for confirming reliability of the supplier's results for ---(b)(4)--- for the ---(b)(4)----- stoppers.

Additional requests/comments

1. 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 -----

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

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.

2. 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.