

# Record of Telephone Conversation, November 8, 2011 - Flublok

Submission Type: BLA   Submission ID: 125285/0   Office: OVRR

Product:

Influenza Vaccine

Applicant:

Protein Sciences Corporation

Telecon Date/Time: 08-Nov-2011 10:19 AM   Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):

1. Information Request

2. Advice

Author: TIMOTHY FRITZ

Telecon Summary:

Fill validation advice and request for information.

FDA Participants: Timothy Fritz

Non-FDA Participants: Penny Post

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

**From:** Fritz, Timothy

**Sent:** Tuesday, November 08, 2011 10:19 AM

**To:** Penny Post (penny.post@proteinsciences.com)

**Subject:** CBER comments regarding Flublok fill validation

**Importance:** High

**Attachments:** CBER fill validation comments\_8 Nov 2011.pdf

Dear Dr. Post-

In light of your plan to execute another fill, we include the following comments regarding material submitted to support fill validation and would like to discuss these by phone prior to your next fill run. Comments regarding other material submitted on 16 September, 2011 will be sent to you at a later date.

1. All CMC issues should be resolved prior to approval. Every Flublok fill run to date has had different problems. Typically we expect completion of 3 successful fill runs, at least one of which is at the proposed commercial scale, prior to approval. Please discuss how you plan to meet these criteria.
2. You attribute failure to achieve the fill target acceptance criteria in PV4 to an incorrect SRID result.
  - a. Inaccuracy and errors in the SRID should be remedied prior to your next fill. Please discuss the steps you have taken to ensure your potency data are reproducible.
  - b. It is critical that you are confident in the accuracy of your assay as lot release samples must achieve release specifications at CBER. We recommend you provide data to demonstrate similarity of results for monovalent and trivalent product tested at PSC, Hospira and CBER prior to initiating your next fill.

c. We request you submit samples from your next fills to CBER for testing. Please make arrangements to ship a suitable number of vials, and discuss testing dates with Dr. Rajesh Gupta.

d. Please provide us with an update on the performance of potency assays you use for the current strains in Flublok, and discuss any problems that you encountered.

e. It is not clear why you would like to change the specification for –b(4)-----  
- Your rationale includes a discussion of B potency assays, but the –b(4)----- data you recently provided show that this is not a problem for rHA of this strain. Regardless, it is unacceptable to increase the specification to any value b(4) Any –b(4)----- result should be considered a potential OOS, with assays repeated. Should OOS be confirmed, an investigation should be conducted, with timely correspondence with the Division of Biological Standards and Quality Control (formerly Division of Product Quality), to alert them of the potential problem and discussion of the potential need for re-assignment of the reference antigen potency value. Similar timely discussions should take place if the sheep antisera do not react as expected with your rHA. It is anticipated that these discussions would take place very soon after potency reagents are available, as they should be tested using product development lots.

f. At the –b(4)-----, potency of H3 was approx 65 µg/mL, but after fill it was 56 µg/mL. Similarly the –b(4)----- had a B potency of 52 µg/mL, but after fill it was 46 µg/mL. Please trend data from all fills to assess whether a loss in potency during the filling process is consistently observed.

3. You have instituted a –b(4)-----  
-" protocol. For discussion, please provide a copy of this SOP and the associated approval document.

4. Please explain the following tests or discrepancies:

a. We understood that your intent was to validate a b(4) fill but the final volume formulated in PV4 was b(4), with much of this volume apparently not filled. Please specify the intended commercial scale at which you will fill. Your fill validation should target this volume, and should demonstrate consistency of fill for this entire volume. Your report should include an accounting of the entire volume, with a record of number of vials filled, volume of blended product used for retains and sampling. Please provide this type of accounting for PV4, and discuss the anomalies.

- b. The batch record of PV4 shows that b(4) full trays of vials were prepared for the fill; only b(4) trays were used.
  - c. The batch record shows –b(4)----- tray labels were rejected, but there is no explanation.
  - d. The –b(4)----- Test Report shows the batch size as –b(4)- but it appears that approx –b(4)---- vials were filled.
  - e. –b(4)----- for PV4 are shown for b(4) vials, suggesting consistent volume is delivered by all needles throughout the run. However, there is inconsistent reporting of volumes; the fill volume shown in the batch record is different from what is shown in the final release sheet; both these values are different from the volume measured in the vials tested at the beginning, middle and end of the run. Please explain. Also, please describe methods in place to measure fill volume at Hospira.
5. Please provide the CoAs for the monovalent bulks used in PV4.

Please submit your responses as an amendment to STN 125285. If you have any questions, please contact the Regulatory Project Manager, Dr. Timothy Fritz, at 301-796-2640.

Thank you.

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