

# Record of Telephone Conversation, May 27, 2011 - Flublok

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Product:  
Influenza Vaccine  
Applicant:  
Protein Sciences Corporation  
Telecon Date/Time: 27-May-2011 02:28 PM    Initiated by FDA? Yes  
Telephone Number: Communicated via e-mail  
Communication Category(ies):  
1. Advice  
2. Information Request  
Author: TIMOTHY FRITZ  
Telecon Summary:  
Comments re Amendments 40, 41 and 43.  
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:** Friday, May 27, 2011 2:28 PM  
**To:** Penny Post (penny.post@proteinsciences.com)  
**Subject:** CBER Advice/Information Request for STN 125285

**Importance:** High

**Attachments:** Information Request 27 May 2011.pdf

Dear Dr. Post-

CBER has reviewed Protein Sciences Corporation's (PSC) January 25, March 9 and April 5, 2011 submissions (Amendments 40, 41 and 43, respectively) to STN 125285 provided in response to CBER's November 12, 2010 Information Request. CBER is providing the following comments and requests regarding these PSC submissions to aid PSC in its response to CBER's January 11, 2010 CR letter:

## Regarding PSC's response to CBER comment 1a (Amendment 41):

- a. Please provide chromatograms, flow rate and pressure for each -b(4)----- column run for both B and H1 processes, and a summary of deviations that occurred during the execution of the reuse protocol.

b. Please note we do not agree with your acceptance criteria of “no negative trends identified.” Please provide column re-use test results with numerical values as acceptance criteria for each parameter and justifications for the numerical values chosen.

**Regarding PSC’s response to CBER comment 2a (Amendment 40).**

You state that you will investigate all future –b(4)-- observed during –b(4)----- analysis. We agree and have reviewed your protocol SOP QT0107 “Characterization of HA samples by –b(4)-----”. Please provide an updated protocol that includes instructions to investigate –b(4)----- . The protocol lists the amount of –b(4)----- . When providing the updated SOP, please correct the amount of –b(4)- to add to the --b(4)----- .

**Regarding PSC’s response to CBER comment 3a (Amendment 41).**

The rHA of A/Perth/16/2009 was used during fill validation PV3. At the date of formulation, potency of this lot was b(4) of release potency, and therefore did not meet requirements previously specified. Please provide the report of this deviation and documentation/batch records that provide instruction on specifications that need to be met before blending.

**Regarding PSC’s response to CBER comment 3b (Amendment 41).**

Stability data for PV2 shows that this lot did not meet potency specifications at 1, 2 and 3 months. The tests were shown to be valid and therefore a deviation was opened. The investigation raises several concerns:

- a. Please provide an explanation or justification for shipping stability samples and product (for transportation validation) via different modes of transportation.
- b. CBER does not consider theoretical shelf life calculated with real time stability data as the method to demonstrate that distributed product meets specifications throughout shelf-life. Rather, manufacturers must review stability data in real time and take immediate action when specifications are not met. Therefore, if –b(4)----- had been distributed, it would have been necessary to file a BPDR and recall product after confirmation of the OOS test result at 4 weeks. Please provide documentation of your recall procedures.

**Regarding PSC’s response to CBER comment 3c (Amendment 41):**

We have reviewed the information you have submitted and do not consider your fill validation to be complete:

We do not agree that 3 vials are representative of approximately –b(4)-- vials filled. Even though the product may be sufficiently blended, data must be provided to demonstrate with sufficient confidence that the process of filling is not detrimental to any product attribute (e.g., volume, appearance, b(4), sterility, identity, potency). CGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§ 211.160(b)(3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)). Please provide results for each of the product release specifications for the number of vials representing fill uniformity with 95% confidence.

a. The data for PV1, PV2 and PV3 provide evidence that the fill process is not sufficiently controlled:

i. PV1 fill failed due to low fill volume. Although this overall problem appears to be corrected, insufficient data are provided to support consistent vial-to-vial fill volume for subsequent fills.

ii. PV2 failed due to inconsistent product stability. Stability samples should be shipped via a validated method, and the SRID assay should be set up in such a way that assay variability is accounted for by the number of replicates and number of vials tested.

iii. PV3 used H3 monovalent bulk that did not meet a specification for formulation. Although this fill lot was not intended for distribution, disregard for all formulation criteria, suggests procedures are not in place to ensure all specifications are met. In addition, invalid test results for H1 and H3 components in many vials tested at release suggest the potency assay is not adequately controlled.

CBER recommends that you establish that all test procedures are reproducible and consistent prior to the next fill validation run. Please provide data to demonstrate each release specification is met with 95% confidence in all vials for one fill at full scale b(4). Stability testing does not need to be performed at this level, but should be conducted at each time point using a number of vials and replicates sufficient to minimize assay variability. A complete batch record for this fill should be included in your response.

b. Should a b(4)batch be targeted for future fills, data to demonstrate fill consistency and product stability at this larger fill volume should be provided in a Prior Approval Supplement (PAS) for 3 consecutive lots after approval of your BLA.

**Regarding PSC’s response to CBER comment 4 (Amendment 43):**

CBER has concerns regarding the follow-up of the –b(4)----- testing results submitted in Amendment 43. The specific details are indicated below. However, since results are pending from ongoing –b(4)----- and PSC studies,



Monovalent bulk stability samples are stored in –b(4)----- of the same material as bulk material. Please provide the surface area to volume ratio for each container.

**Regarding PSC’s response to CBER comment 7b (Amendment 41):**

Stability data of the formulated product support a 16 week shelf life, but data for Perth/16 H3 monovalent bulk shows poor stability as the product did not meet the requirement for b(4) of release potency –b(4)----- after manufacture. We note that PSC aims to increase this stability by improving storage conditions. We recommend you submit data to support change in –b(4)----- as a PAS, unless it is necessary to use these conditions to formulate with H3 Perth/16, in which case the data should be submitted in response to this comment as soon as possible. This should include data to demonstrate changed conditions do not impact process step performance (---b(4)-----) and product quality (in particular, monovalent bulk potency – b(4)-----), that there is no impact of the –b(4)----- on in-process or release test methods (in particular, SRID, total protein and purity assay accuracy), container leachable/extractables, and data supporting improved stability of drug substance under these conditions. Data should be provided for each HA type that will be stored under the revised conditions. PSC also needs to reassess cleaning validation for product contact equipment, provide evidence that the –b(4)----- raw material is tested for identity/purity, have a validated method to quantify –b(4)----- and establish a specification for –b(4)----- in final product. Information pertinent to product safety and immunogenicity using the –b(4)----- should also be included in such a PAS..

**Regarding PSC’s response to CBER comment 7c (Amendment 41):**

PSC did not open a deviation report at the time lots were substituted for stability testing due to a storage b(4) leakage. Please provide evidence that you have implemented all corrective actions noted in your November 13, 2009 response to FDA Form 483, item 2.

**Regarding PSC’s response to CBER comment 7e (Amendment 41):**

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Concerning shipping validation, please clarify if there was a temperature excursion associated with trip number 49214689. If this was an excursion, please provide the deviation and subsequent investigation.

Please submit your responses as an amendment to STN 125285. We recommend that you restate each item and follow it with your explanation or clarification. Use of this

format helps organize the relevant information and provides a self-contained document that facilitates future reference.

If you have any questions, please contact the Regulatory Project Manager, Dr. Timothy Fritz, at 301-796-2640.

Thank you.

Timothy A. Fritz, Ph.D.

Microbiologist

FDA/CBER/OVRR/DVRPA/CMC2

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