

RECORD OF TELEPHONE CONVERSATION

Submission Type: Original Application Submission ID: 125285/0 Office: OVRR

Product:
Influenza Vaccine

Applicant:
Protein Sciences Corporation

Telecon Date/Time: 30-JUL-2009 09:12 AM Initiated by FDA? Yes
Fax Number: 203-686-0268

Communication Category(ies):
Information Request, Advice

Author: TIMOTHY FRITZ

Telecon Summary:
CMC information request and advice regarding the sponsor's response to CBER's Complete Response letter of August 29, 2008.

FDA Participants: Timothy Fritz

Non-FDA Participants: Drs Manon Cox

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:
Regarding your response to comment 1 (Process Validation):

1a. Concerning process validation:

- A) We note from the 2008 manufacturing campaign that approximately 50% of lots were terminated. Please describe changes implemented to enhance manufacturing consistency and indicate if these corrective measures were in place prior to the 2009 campaign.
- B) Concerning the 2008 Process Validation Report (R-09-005) for H3: we note that an H1 batch (-(b)(4)-) was manufactured between process validation runs for

H3. The H1 batch (---(b)(4)---) was terminated due to -----(b)(4)----- and irregular column performance. Please provide an assessment of the impact of this deviation on the H3 process validation study.

C) The following information is requested for complete review of your process validation of the H3 component in 2009:

- a) -----(b)(4)-----:
- i. -----(b)(4)-----
-----.
 - ii. -----
----- (b)(4) -----
-----.
 - iii. -----

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

-----.
 - iv. ----- (b)(4) -----
-----.
- b) ----- (b)(4) -----:
- (b)(4) -----
-----.
- c) ----- (b)(4) -----:
- i. -----
----- (b)(4) -----
-----.
 - ii. ----- (b)(4) -----
-----.
 - iii. ----- (b)(4) -----
-----.
 - iv. -----
----- (b)(4) -----
-----.
 - v. ----- (b)(4) -----
-----.
- d) ----- (b)(4) -----:
- i. ----- (b)(4) -----
-----.
 - ii. -----

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

-----.

1 page redacted (b)(4)

- A) -----
----- (b)(4) -----
-----.
- B) -----
----- (b)(4) -----
-----.

2g. Concerning re-use of columns:

- A) In your lifetime studies for the (b)(4) and (b)(4) columns, please provide data for protein load capacity and linear flow rate.
- B) It is unclear if cleaning, sanitization and storage procedures used in your scaled-down study for the (b)(4) and (b)(4) columns are the same as those used in your commercial scale purification process. Please clarify.
- C) Please provide data for ----- (b)(4) ----- in your lifetime studies to support cleaning and sanitization of the (b)(4) and (b)(4) columns.
- D) We note that you recycle - (b)(4) - columns even when there is strain change. Please provide data to support the absence of any product from the prior run in the eluate and state how this type of contamination is controlled during manufacture.
- E) The data shown in Table 2g-2 suggests step (b)(4) is reduced when the packed column is used ----- (b)(4) ----- (note reduced ----- (b)(4) -----). Please include a specification to ----- (b)(4) -----.
- F) Table 2g-5 (--- (b)(4) --- column re-use) shows purification of different strains using the same column. Please provide data to support the absence of material from previous runs in the eluate, and state how this type of contamination is controlled during manufacturing runs.

Regarding your response to comment 3 (Product Specifications):

3a. Concerning product potency:

You have used stability study results to estimate the actual potency of each strain in vaccine lots on the median day of vaccination in four clinical trials. This provides a basis to revise the minimum dose proven efficacious in human trials. You conclude that the clinical data support a minimum potency value of --- (b)(4) --- per strain and a 16 week shelf-life of FluBlok. Please address the following issues:

- A) -----

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

- B) -----

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

- C) Actual potency at time of vaccination during clinical studies was based on the median day of vaccination. This assumes that individuals vaccinated in early and

D) Your current estimates for potency at day of vaccination (Table 3a-1) indicate that the vaccines given in most clinical trials contained significantly more than (b)(4) of B HA antigen per dose (lower confidence limits greater than (b)(4)). If revisions to estimates of actual potency are made, please set the minimum expiry potency of each antigen to a level with demonstrated clinical efficacy.

A) You anticipate that a specification of (b)(4) per rHA antigen per dose can be met through 16 weeks by formulating FluBlok at -----(b)(4)----- in relation to the label claim of 45 µg per antigen. You predict that (b)(4) product to --(b)(4)-- antigen per dose will ensure potency at product release of --(b)(4)-- dose. Shelf-life determinations are calculated based on this assumption, but the assumption is not acceptable unless the product release specification is --(b)(4)-- dose. Please provide the current minimum release specification for potency.

C) _____

 _____(b)(4)_____

B) Please provide an updated table to show your batch formula (note that in your original submission, Table 3.2.P.3.2.-1 included incorrect units).

3g. *Regarding DNA concentration and -----(b)(4)-----:*

- A) Please state whether -----(b)(4)----- is diluted for total DNA quantitation and provide an explanation of how DNA per dose was calculated for each preparation.
- B) -----

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

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

-----.

Regarding your response to comment 4 (Stability):

4a. Concerning the presence of particles in some monovalent bulk batches:

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

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

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

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

4c. Concerning stability tests of drug product:

- A) Stability test results were provided for FluBlok batch ---(b)(4)--- and Hospira method numbers were listed.
- a) Please state where the stability study is performed. If the study is performed at Hospira, please provide results to support equivalence of BCA assay at Protein Sciences and Hospira.
- b) Please specify the number of samples and number of replicates of each sample that are tested in each assay.
- c) The variability of results reported for BCA assay is not satisfactory. Criteria should be established to reduce assay variability. Please comment.

- d) Parameters that allow more frequent tests (or repeat tests) should be implemented when results are out-of-trend. Please state whether your stability protocol has provision to evaluate out-of-trend results.
- B) Regarding stability study of FluBlok batch ---(b)(4)---: The differences measured in total protein are greater than the variability in the validated assay, and therefore may reflect variations in the filled vials. Please evaluate vial-to-vial variation in total protein concentration to establish the number of replicate samples to be measured at each time point.

4d. Concerning stability of monovalent bulks:

- A) ----(b)(4)---- of 2007 drug substance show that the H1 Solomon Islands but not H3 or B contains HA1 and HA2 (Figure 4d-2). Please provide ----(b)(4)---- for 2009 H1, H3 and B lots in addition to -----(b)(4)----- of each lot.
- B) Table 4d-9 indicates that stability tests of 2008 rHA monovalent bulks did not begin at substance release. Since previous studies show substantial loss of potency within the first --(b)(4)--, stability studies that begin after the release date may be misleading. In your stability protocol, please define the time between substance/product release and day 0 of drug substance and drug product stability study.
- C) We disagree with your statement that the rHA monovalent bulk drug substance is stable for at least --(b)(4)--. The data show that the drug substance is not stable but can meet requirements when starting concentrations and -----(b)(4)----- are sufficiently high at release. Please re-evaluate the specification of -----(b)(4)- ----- after each manufacturing campaign to improve consistency and shelf-life of the monovalent bulk.
- D) Please provide the ---(b)(4)--- and ---(b)(4)--- analysis performed on 2008 rHA batches placed on stability studies at release, day 0 of the stability study and at 3 months.

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

5c. Concerning the ----(b)(4)----- assays (Section 3.2.A.2.2 Viral):

(b)(4)

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

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

B) -----(b)(4)-----:
a) -----(b)(4)-----

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

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

-----.

(b)(4).

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

-----.

A) -----

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

-----.

B) -----

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

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Regarding your response to comment 8 (In-process Tests):

8b. Concerning bioburden tests:

Please state the rationale for making a (b)(4) dilution before (b)(4).

8c. Concerning removal of --(b)(4)--:

Please provide data to support removal of ----- (b)(4) -----
----- steps.

Regarding your response to comment 9 (Baculovirus Clearance):

The titers of baculovirus in the starting material (-(b)(4)-) range from ----(b)(4)---- per
dose. Your studies show clearance of at least -----(b)(4)-----, -----
