

12/10/2010

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**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

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**Meeting Type/Category:** Type C Meeting (-----)(b)(4)-----)

**Meeting Date/Time:** December 10, 2010, 3:30-5PM

**Product:** Influenza Vaccine

**Received Briefing Package:** December 9, 2010

**Sponsor:** Protein Sciences Corporation

**Meeting Chair:** Timothy A. Fritz

**FDA Attendees:** Wellington Sun  
Loris McVittie  
Arifa Khan  
Maryna Eichelberger  
Jerry Weir  
Rajesh Gupta  
Deborah Trout  
Rakesh Pandey  
Timothy Fritz

**Sponsor Attendees:** Drs Manon Cox, President and CEO  
Penny Post, Vice President, Regulatory and Quality  
Clifton McPherson, Director, Quality Control  
Peter Cardinal, Director, Validation  
Albert Price  
Yoshi Hashimoto  
Joe Rininger, Senior Director, Influenza  
Elena Feshchenko

**BARDA Representatives:**

Tanima Sinha  
Susan Zhao  
Lou Mocca  
Armen Donabedian

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## BACKGROUND

CBER issued Protein Sciences Corporation (PSC) an Information Request (IR) on November 12, 2010 regarding PSC's responses to CBER's January 11, 2010 Complete Response Letter. CBER had indicated in an earlier telecon that, if needed, a telecon could be scheduled to address questions PSC may have regarding the November 12, 2010 IR. A telecon was scheduled for December 10, 2010 and on December 9, 2010 PSC provided CBER a list of questions to be discussed. It was agreed to discuss the following items from CBER's November 12, 2010 IR letter: Comment 3c, Comment 4 (all subparts), Comment 7b, Comment 8e and Comment 8f, parts i and ii.

Information provided by PSC and PSC's questions are provided below. Discussions regarding PSC's questions are shown in indented, bold italics:

## QUESTIONS AND DISCUSSIONS

**Comment 3c. Vial-to-vial consistency in fill.** Please provide clarification. Data were provided to support consistency of fill for PV runs #1 and #2 in the June 29, 2010 BLA submission. Is this comment specific to data from PV run #3?

**Discussion:** CBER said that its comment was not specific to Process Validation (PV) run #3 but pertained to each PV run. CBER also said that fill volume information alone was insufficient and that PSC needed to provide information for each release specification (i.e., potency, (b)(4), ---(b)(4)---, etc). PSC said that it had provided potency information for the beginning, middle and end of the production process. CBER requested that PSC indicate which submission contained that information. PSC asked if sampling of 3 vials from the various production stages was sufficient. CBER replied that sampling of 3 vials was not sufficient, that PSC should sample a statistically representative number of vials and provide a statistical justification for the number of vials to be tested. PSC noted that its SOPP for process validation had been submitted to CBER.

**Comment 4. -----(b)(4)-----:** Is our assumption correct that the experimental work proposed under a.ii. and a.iii. is not required in the event a.i. experiments reveal -----

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**Discussion:** *CBER Response: Yes.*

## Background

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**Comment 7b. Stability:** Regarding formulation development, we plan to submit a summary of our work to date and our plans for going forward in our response to the IR letter. Please clarify whether extension of our currently proposed shelf life (16 weeks) is necessary prior to licensure or whether evidence that we can meet our proposed shelf life is sufficient for initial BLA approval. What type of changes in formulation would require additional clinical studies?

***Discussion:*** *CBER said that it was not suggesting an extension of the current 16 week FluBlok shelf life but that it wanted to make sure that the FluBlok product will meet release specifications. PSC said that it would submit the summary of the FluBlok formulation development. Regarding changes in formulation that would require additional clinical studies, CBER said that it would need to review the actual changes prior to making a decision.*

**Comment 8e. Immunogenicity of A/California/07/2009 rHA in Mice:** We have designed a follow-up mouse immunogenicity study to support initial conclusions about the immunogenicity of the A/California/07/2009 rHA. The study we have designed will compare the following:

- 1) Two trivalent formulations of rHA: one containing A/Brisbane/59/2007 rHA (with known potency by SRID assay) and one containing A/California/07/2009 rHA and;
- 2) A 2010/2011 licensed formulation (Flulaval) trivalent product containing A/California/07/2009.

If comparable immunogenicity is observed with A/California/07/2009 rHA to the licensed product, will that provide sufficient evidence to support conclusions of the immunogenicity for A/California/07/2009 rHA?

In addition, we also intend to provide serological data from a human clinical dose escalation study conducted in Australia with A/California/04/2009 rHA by —b(4)-----, to support immunogenicity.

***Discussion:*** *CBER said that because there is no validated mouse immunogenicity model, it would be difficult to use mouse immunogenicity data to support human immunogenicity. However, CBER said that PSC could submit the data and that CBER would discuss the results internally.*

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**Comment 8fi. SRID for A/California/07/2009:** Please clarify your intention to recalibrate the stated potency of CBER SRID reagents for H1 A/California/07/2009. Will potency be assigned based on the rHA antigen content of PSC's bulk drug substance? Will this recalibration be based on total rHA content as measured by total protein and purity? One of the issues relating to quantitation of PSC's rHA for A/California was poor ring quality when using antiserum derived from egg-based product. Is CBER considering generating antiserum against our rHA protein? What is the timeline for this process, and will this impact release of 2011 batches? Who will serve as the contact person at CBER for continued discussions on this topic, if necessary?

***Discussion:*** CBER said that it would calibrate PSC's monovalent bulk material as a Primary Liquid Standard (PLS) based on total protein content and SDS-PAGE analysis. Using that PLS, CBER would optimize the concentration of CBER's H1N1 serum to produce a measurable SRID ring. Then, CBER would try to recalibrate CBER's egg grown reference antigen against PSC's PLS using the optimized concentration of CBER's H1N1 antibodies. If technical problems are encountered in calibrating CBER's egg grown reference antigen due to low HA content per vial, CBER will prepare a small lot of lyophilized reference antigen from PSC's monovalent bulk material and calibrate the lyophilized material against PLS using the optimized concentration of CBER's H1N1 antibodies. The latter approach may have problems if there are stability issues with PSC's material. PSC indicated that their monovalent bulks are stable when they contain -----(b)(4)-----.

***CBER said that it would not raise antisera against the PSC antigen.***

***CBER indicated that it would take approximately 3 weeks after receipt of material from PSC to determine if recalibration of CBER potency reagents was acceptable. CBER said that PSC should submit its samples to Manju Joshi at CBER using the address for Manju Joshi that CBER had previously provided to PSC. CBER also said that PSC could correspond via e-mail with Rajesh Gupta regarding the progress of the recalibration experiments.***

***PSC asked whether these would be approved reagents. CBER replied that if the calibration process described above works successfully, these reagents could be used for lot release.***

**Comment 8fii A/California/07/2009 Antigenic Structure:**

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**Additional Discussion:**

*CBER provided PSC with a reference (-----b(4)-----) regarding sample preparation for the (b)(4) assay.*

*CBER also said that PSC should submit stability data for PV run #3 even though a validated assay for H1 component is not in place because this will provide stability data for the H3 component that is of some concern to CBER.*

*PSC asked if they should communicate directly with the CBER reviewers when providing information to CBER. CBER indicated that PSC should not communicate with the reviewers directly but should continue to provide information for reviewers through the Regulatory Project Manager.*