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DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS**

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Subject: FDA/Sponsor Final Meeting Summary

Dear Drs Cox:

Attached is a copy of the memorandum summarizing your April 12, 2010 BLA meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the outcome differs from those expressed in this meeting summary, it is your responsibility to bring these discrepancies to CBER's attention for resolution.

Please use the above reference tracking numbers for all future correspondence and submissions.

If you have any questions, please contact Timothy A. Fritz at (301) 827-3070.

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FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Meeting Type/Category: BLA Meeting

Meeting Date/Time: April 12, 2010, 2–3:30 PM

Application Number: CRMTS 7416

Product: Influenza Vaccine

Received Briefing Package: March 15, 2010

Sponsor: Protein Sciences Corporation

Meeting Chair: Rakesh Pandey, OVRR

FDA Attendees: Jerry Weir, OVRR
Maryna Eichelberger, OVRR
Matthew Sandbulte, OVRR
Arifa Khan, OVRR
Deborah Trout, OCBQ
William McCormick, OVRR
Cynthia Nolletti, OVRR
Lewis Schrager, OVRR
Keith Peden, OVRR
Hana Golding, OVRR
Katherine Matrakas, OVRR
Timothy Fritz, OVRR

Sponsor Attendees: Manon Cox, President and CEO
Dan Adams, Executive Chairman
Penny Post, VP, Regulatory and Quality
Mark Michalik, VP, Operations
Clifton McPherson, Director, Quality Control
Peter Cardinal, Director, Validation

Sponsor Consultants: -----(b)(4)-----

BARDA Attendees: Lou Mocca

Frank Arnold
Sheng Li

BACKGROUND:

CBER issued Protein Sciences Corporation (PSC) a Complete Response (CR) Letter on January 11, 2010. PSC requested a Type C meeting to discuss the CR Letter. A meeting was scheduled for April 12, 2010 and PSC provided CBER with a briefing package containing questions concerning the CR Letter items on March 15, 2010. CBER provided PSC with a response to their questions on April 9, 2010. PSC's briefing package questions and CBER's response are included as an appendix at the end of these meeting minutes.

DISCUSSION:

PSC provided CBER with a 1 page handout containing a timeline showing PSC's estimate of when responses to the CR Letter items would be provided to CBER. The timeline indicated that responses for CR Letter items 1, 3, 4, 5, 6, 7 and 8 were targeted for submission to CBER by the end of June, 2010. The information for CR Letter item 1 would contain ---(b)(4)--- stability data for the B strain, ---(b)(4)--- stability data for the H1 strain and preliminary batch data for Drug Product fill validation lot 3 (PV3). An update to the information for CR Letter item 1 would be provided to CBER in late September. The timeline also indicated that a strain change supplement for the 2010/2011 season was targeted for submission to the FluBlok BLA in mid-July.

PSC began the discussion by saying that they would like to receive further clarification of CBER's responses to questions 5, 7, 8, 9 and 10 and noted that the most important issue for discussion concerned -----(b)(4)----- . The list of questions and the discussion is presented below.

Briefing Package Question 5b

Discussion: PSC noted that the rHA B strain process had been validated and that if the same process change is demonstrated for the rHA H1 strain, H1 process validation will include the change control.

Briefing Package Question 5c

Discussion: PSC noted that CBER's response incorrectly indicated that the ---(b)(4)----- for the B strain varied from ---(b)(4)----- . The actual variability in the -----(b)(4)----- for the B strain varied from ----(b)(4)----- as shown on page 31 of the briefing package. CBER acknowledged the mistake. PSC said that -----(b)(4)----- for the rHA B strain produced in the recent validation runs is more consistent.

Briefing Package Question 7 (Reagents for process validation testing)

1 Page determined to be not releasable: b(4)

CBER noted that the timeline provided by PSC did not indicate when final stability data for fill validation lot 2 (PV2) would be submitted. PSC said that 3 month stability data for PV2 would be provided at the end of June and 3 month stability data for fill validation lot 3 (PV3) would be provided at the end of September. CBER noted that it would need stability data for PV2 and PV3 up to the expiry date (i.e., 16 weeks). PSC said that 16 week stability data for PV2 and PV3 would be ready at the end of July and at the end of October, respectively.

CBER asked whether PV2 was done at full-scale. PSC said that PV2 was done at a full-scale of ----(b)(4)-----.

CBER reminded PSC that at the beginning of each new manufacturing campaign (at strain change or after a significant break in manufacturing, e.g. the beginning of each seasonal cycle) samples from 3-5 monovalent lots should be submitted to CBER for potency testing. CBER mentioned that PSC's plan to test its fill validation lots with (b)(4) reagents instead of CBER reagents was not without risk and that a larger risk was associated with potential differences in testing egg-based versus cell-based flu antigens using egg-based flu reagents. CBER informed PSC that when CBER reagents become available, PSC must begin potency testing using CBER reagents. PSC must ensure that for lots in which stability testing was begun using (b)(4) reagents, enough (b)(4) reagents are available to finish the stability testing. CBER indicated that CBER potency reagents were expected to be ready in mid-May 2010.

PSC asked whether the (b)(4) reagents were more appropriate for testing FluBlok since the (b)(4) reagents were developed using the A/Perth H3 strain. CBER noted that the (b)(4) reagents were developed using the A/Wisconsin/15/2009 H3 strain. CBER reagents are derived from the A/Victoria/210/2009 H3 strain. Both the (b)(4) and CBER H3 strains are A/Perth/16/2009-like.

CBER noted that PSC had submitted improperly or unlabeled samples for testing to CBER and that PSC could contact CBER prior to submitting samples for clarification as to how the samples should be labeled to ensure appropriate testing.

APPENDIX: (PSC's briefing package questions and CBER's April 9, 2010 response)

Protein Science Corporation's questions are presented below followed by CBER responses in bold.

General:

1. PSC proposes to submit responses to individual CR letter items as they are completed, in a rolling format, in order to expedite the review process. We anticipate submissions to be made no more frequently than monthly. While we understand that the response will not be considered complete until the last item has been submitted, we envision that this mechanism facilitates a more rapid review. Would this be acceptable to the Agency?

CBER Response: CBER recommends that any submissions made in response to the January 11, 2010 CR letter in a rolling format contain a complete response to the CR letter item(s) addressed in the submission and that responses to individual CR items not be spread over multiple submissions. It would be helpful for PSC to provide CBER a timeline in advance for when complete responses for each CR item are expected.

2. PSC's objective is to complete its response to the CR letter by mid-June 2010, pending the Agency's feedback during this meeting. Can the Agency clarify whether it will need the entire 6-month review timeline or whether review under a more accelerated timeline will be possible?

CBER Response: We cannot predict the time needed to review the Complete Response in advance of its submission. Upon receipt of a Complete Response, CBER will complete its review of submitted material as soon as possible within the time allowed under PDUFA guidelines.

3. Does the Agency have additional comments or recommendations on the proposals and strategies presented in the meeting information package that are intended to address the outstanding CMC issues needed for licensure of FluBlok?

CBER Response: CBER does not agree with PSC's decision to re-designate the rHA of the influenza B strain as B/Brisbane/33/08. The strain designation provides important information regarding the derivation of the WVB and the passage history of the CDC reference strain from which the gene originated. Therefore, CBER recommends retaining the B/Brisbane/60/08 strain designation. Assuming the data PSC plans to provide demonstrates antigenic similarity to the reference strain B/Brisbane/60/08, there would be no cause for objection to your B rHA sequence.

Process Validation (Item 1, 11 Jan 2010 CR Letter):

4. FDA's January 11, 2010 CR letter comment 1a focuses on issues relating to the manufacture/purification of the HA from B/Brisbane/33/2008 (refer to footnote 1 on page 1 of this document). CBER's comment, however, references the final 2009 H3 Process Report

(R-09-036). Can the Agency please clarify that comment 1a refers to the FluBlok Downstream Process Validation Report for rHA B strains, i.e., HA from B/Brisbane/33/2008 and not the H3 Process Validation Report (R-09-005)?

CBER Response: PSC is correct that comment 1a of the January 11, 2010 CR letter refers to the FluBlok Downstream Process Validation Report for rHA B strain and not the H3 strain.

5. Background information regarding our plan to resolve the inconsistencies in yield and for rHA B strains (January 11, 2010 CR letter comment 1a) and the approved validation protocol are included in the Background Section of this meeting briefing document.
 - a. Does FDA have comments regarding the protocol or specific comments on the submitted data or its interpretation?

**CBER Response: The information provided in the briefing document should be included in your complete response together with CC-10-019 and any validation data (e.g., compatibility, extractable and potential leachables) to support the change. If not in the change control document, please also provide information that addresses changes in quality of rHA resulting from the change in -----(b)(4)-----
----- Stability results of the 3 validation lots should be provided. Please provide similar information for other strains if this -----(b)(4)-----
----- change will also be implemented for H1 and H3 purification.**

Please note that a change control system should evaluate and approve proposed changes to specifications, test procedures, raw materials, facilities, support systems, equipment (including computer hardware), processing steps, packaging materials, and computer software. Changes could be categorized as minor or major depending on the nature and extent of the changes, and the effects these changes could impart on the process. In all cases, scientific judgment should determine what additional testing and validation studies are needed to justify a change in a validated process.

- b. Does successful execution of this protocol remove process consistency concerns for the B strains?

CBER Response: We agree.

- c. Can the agency please clarify the concern around ---(b)(4)----- for rHA B strains?

CBER Response: The ---(b)(4)----- data previously provided for B validation lots has shown significant variability ----(b)(4)----. Following the changes in -----(b)(4)----- you have implemented, the ---(b)(4)----- measured for the engineering run monovalent bulk appears to be acceptable. CBER's concern regarding the ---(b)(4)----- for PSC's rHA B strains should be adequately addressed if (b)(4) similar to that measured for the engineering run are attained during the 2010 validation runs.

6. Comment 1b of the January 11, 2010 CR letter is directed towards issues identified in the downstream processing of the manufacture of rHA derived from H1 A/Brisbane/59/2007. PSC has made improvements in (b)(4) column performance for the purification of the H1 rHA. The FDA VRBPAC recommended that A/California/07/2009 replace A/Brisbane/59/2007 as the recommended H1N1 vaccine strain. As a result, we propose to address this comment by re-validating the rHA H1 process using rHA derived from A/California/07/2009. A protocol similar to that for the B strain process validation (**Attachment 1** of this document) will be used. Does the Agency concur that this is an acceptable approach? If not, what additional or replacement steps does CBER recommend?

CBER Response: Because data provided in PSC's December 11, 2009 submission (including Reports 09-073 and 09-075) do not support consistent (b)(4) chromatography for purification of H1 hemagglutinin, we request a report of investigations that were done to identify the root cause(s) of discrepancies in (b)(4) column performance. This report should be completed prior to conducting the proposed H1N1 validation runs and should include:

- **An assessment of differences in elution profiles for 2009 H1 validation runs**
- **A reassessment of investigation 09-073**
- **A reassessment of the out-of-trend potency result for lot --(b)(4)---**
- **The report should describe corrective actions that have been implemented to ensure consistent (b)(4) column performance.**

We concur with the plan to validate the H1 process using A/California/07/2009. If changes to the process were introduced, please include relevant data to support the change (process development data or change control documentation).

7. PV2 (process validation run 2 for formulation and filling) has been filled at Hospira using rHAs derived from A/Brisbane/10/2007, A/Brisbane/59/2007, and B/Brisbane/33/2008. Data from PV2 will be included in our response to the CR letter. We are in the process of finalizing the fill date for PV3 at Hospira and we plan to complete this fill with rHAs derived from strains in compliance with those recommended for the 2010/2011 vaccine composition (A/California/07/2009, A/Perth/16/2009, B/Brisbane/33/2008). Data from this run will be submitted as soon as it becomes available. We plan to formulate PV3 using reagents from (b)(4) in lieu of having CBER H3/Perth SRID reagents. Is this an acceptable approach or does the Agency prefer that PSC waits until H3/Perth reagents will be available?

CBER Response: We agree with the use of the 2010/2011 formulation for PV3. CBER SRID reagents for A/Perth/16-like virus are scheduled to be available for distribution in mid-May. The CBER antigen for this reagent set is, in fact, made from the NYMC X-187 reassortant based upon A/Victoria/210/2009 as this is the dominant candidate strain for use in vaccine manufactured for distribution in the US. In this case CBER finds it acceptable, but not without risk, to use the (b)(4) reagent set for PSC's H3/Perth-like strain until the CBER reagents become available. No manufactured lot will be released for distribution until (b)(4) and CBER reagents are shown to be equivalent and appropriate for testing PSC HAs.

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

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

c) -----

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

-----.

d) -----

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

e) -----

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

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(b)(4) Assays for Adventitious Agent Testing (Item 3, 11 Jan 2010 CR Letter):

9. -----

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

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

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

Particle Characteristics (Item 4, 11 Jan 2010 CR Letter):

10. Data generated to date to evaluate particle characteristics are provided in the meeting briefing package as well as the plans for further study. Does the Agency have any comments on this information or on the proposed additional studies?

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

**CBER Response: Based on the results provided or summarized in the text of your brief report, these analyses appear useful in characterizing the physical nature of the recombinant antigens. Your complete response should include the full report on -----
----- (b)(4) -----

-----.**

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

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Product Purity (Item 7, 11 Jan 2010 CR Letter):

11. Does the Agency have any comments on the product purity information submitted to the BLA on December 18, 2009 regarding purity assay validation, (b)(4) testing to confirm ----(b)(4)-----, validation of Tween-20 assay, and ----(b)(4)----- DNA assay validation? Does this response adequately address CR Comment 7? If not, please specify the concerns.

CBER Response: PSC's December 18, 2009 submission regarding purity assay validation, --(b)(4)-- testing to confirm removal by ---(b)(4)----, validation of the Tween-20 assay and ---(b)(4)----- DNA assay validation is acceptable.

Outstanding Inspectional Issues (Item 8, 11 Jan 2010 CR Letter):

12. PSC received feedback from CBER (teleconference of February 4, 2010 with Debbie Trout and Maryna Eichelberger) on the responses PSC submitted November 13, 2009, to the Form 483 received October 23, 2009, following the pre-licensure re-inspection of October 19-23, 2009. PSC anticipates submitting revised responses the week of March 15. Does FDA have any additional comments regarding inspectional observations and PSC's responses to the October 2009 pre-licensing inspection?

CBER Response: We look forward to receipt of stability SOPs and your responses to observations 2, 4, and 7.