

**CENTER FOR BIOLOGICS EVALUATION RESEARCH AND REVIEW
OFFICE OF VACCINES RESEARCH AND REVIEW
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 September 24, 2009 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 up to and including your initial IND submission.

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: September 24, 2009, 3–4 PM

Application Number: CRMTS 7226

Product: Influenza Vaccine

Received Briefing Package: September 3, 2009

Sponsor: Protein Sciences Corporation

Meeting Chair: Norman Baylor, OVRR

FDA Attendees: Karen Midthun, OD
Robert Yetter, OD
Norman Baylor, OVRR
Wellington Sun, OVRR
Loris McVittie, OVRR
Marion Gruber, OVRR
Maryna Eichelberger, OVRR
Matthew Sandbulte, OVRR
Arifa Khan, OVRR
Mary Malarkey, OCBQ
Carolyn Renshaw, OCBQ
Deborah Trout, OCBQ
John Eltermann, OCBQ
Cynthia Nolletti, OVRR
Lewis Schrager, OVRR
Barbara Krasnicka, OBE
Lev Sirota, OBE
Phillip Krause, OVRR
Rajesh Gupta, OVRR
Rakesh Pandey, OVRR
Timothy Fritz, OVRR

Sponsor Attendees: Dan Adams, Chairman, President, and CEO
Manon Cox, Chief Operating Officer
Penny Post, VP, Regulatory and Quality
Mark Michalik, VP, Operations
Clifton McPherson, Director, Quality Control

Peter Cardinal, Director, Validation
Kathy Holtz, Scientist and Project Manager Influenza
Jason Hollister, Scientist and Technical BLA Writer

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

-----**(b)(4)**-----
-----**(b)(4)**-----: -----**(b)(4)**-----Consultant

BARDA Attendees: Maurice Harmon
Frank Arnold

BACKGROUND

Protein Science Corporation (PSC) was notified on August 7, 2009 of FDA's decision that it would not present FluBlok at the September 11, 2009 Vaccines and Related Biologics Products Advisory Committee (VRBPAC). PSC contacted CBER to inform them of its concern that FluBlok would not be presented at the September 11, 2009 VRBPAC. CBER management recommended that PSC request a meeting with CBER to discuss unresolved CMC and other issues affecting BLA approval. A meeting between CBER and PSC was scheduled for September 24, 2009 and meeting materials with questions was received from PSC on September 2, 2009. CBER submitted a response to PSC's questions on September 23, 2009. PSC's questions and CBER's response are included as an appendix to these meeting minutes.

DISCUSSION

CBER began the meeting by indicating that CBER wanted to move the BLA review/approval process forward. However, since CBER had provided PSC a response to its meeting material questions and was drafting an Information Request for PSC, certain details might not be discussed at the meeting. CBER noted that FluBlok process validation is important and that the approval process could not move forward without assurance that FluBlok can be manufactured consistently.

PSC indicated that they wanted to have more certainty regarding the issues that remain a concern to the FDA.

CBER suggested that PSC seek clarification on any of the statements submitted by CBER in response to PSC's meeting material questions.

Question 1. Process validation

1a-c: PSC did not request further clarification.

1d: PSC asked whether the additional data sought by CBER to support the bulk filtration step included information such as flow rates and---(b)(4)--- testing. CBER indicated yes and that PSC would need to set parameters for these values in the Batch Production Record.

CBER also stated that parameters should be set for time, temperature and any product sampling performed (e.g., bioburden) prior to filtration.

- 1e:** PSC did not request further clarification.
- 1f:** PSC noted that it did not show purification at the -----(b)(4)-----
----- (b)(4)----- steps and asked CBER whether these were the steps CBER sought additional information regarding product purification. CBER indicated that PSC should identify the effect of these steps on product purity and demonstrate consistent purification at this/these step(s).
- 1g:** PSC did not request further clarification but noted that there was no hold time between -----(b)(4)-----.
- 1h:** PSC requested further clarification regarding Drug Substance hold time. CBER indicated that this is synonymous with drug substance shelf life, and that drug substance stability data should be used to support this hold time/shelf life.
- 1i:** PSC did not request further clarification.
- 1j:** PSC noted that it stored columns in -(b)(4)-. CBER stated the IR response was unclear because -----(b)(4)----- were not assessed to support cleaning and sanitization of the columns prior to use.
- 1k:** PSC noted that acceptance criteria had been set and asked CBER what additional information was needed. CBER indicated that its recommendation was for PSC's internal information and that no further information will be requested.
- 1l:** PSC noted that it has batch records for visually confirmed parameters which are done as a check-off. CBER noted that when parameters are not electronically recorded, it would be beneficial to document the measurements instead of checking them off. No further information will be requested.
- 1m and u:**
PSC noted that it was concerned with its -----(b)(4)----- and it would fix the problems associated with this step. PSC also stated that they had approval from the Director of Quality to -----(b)(4)----- . CBER informed PSC that they did not provide the necessary documentation to support this statement.
- 1n-p:** PSC did not request further clarification.
- 1q:** PSC requested further clarification and CBER noted that the details regarding the additional information it needed would be included in the pending Information Request.
- 1r:** PSC did not request further clarification.
- 1s:** PSC asked CBER to confirm that the specification for Triton X-100 should only be based on results from the 2008 season. CBER concurred.

ADDITIONAL DISCUSSION

CBER noted that the 4 month shelf life for FluBlok was unusual and asked whether PSC would be collecting additional stability data. PSC acknowledged that the shelf life was unusual and that it was evaluating alternative assays to monitor stability (e.g.------(b)(4)-----, -----(b)(4)----) and also evaluating -----(b)(4)-----) to increase FluBlok stability. CBER asked whether instability was also observed in monovalent bulks. PSC indicated that instability was observed in monovalent bulks.

CBER asked whether PSC has observed changes in safety or immunogenicity of FluBlok due to instability. PSC indicated that it had investigated this and that, though not statistically significant, it appeared that FluBlok became more immunogenic as it decayed but that it was not more reactogenic.

CBER reiterated that it was important that PSC understand the cause of FluBlok's instability and that if a closed VRBPAC session was needed, CBER would need to communicate its concerns to the Advisory Committee. PSC asked when CBER could complete its review of PSC's response to the pending Information Request. CBER noted that it could not provide a specific date due to the unknown volume of unrelated work it would be receiving.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Information Request	CBER	As soon as possible. Target is the week of September 28, 2009.
Response to CBER Information Request	PSC	As soon as possible.

APPENDIX (PSC questions and CBER response for September 24, 2009 meeting)

Dear Dr. Post-

We have reviewed your September 3, 2009 pre-read materials for the September 24 meeting with CBER to discuss outstanding issues related to your FluBlok BLA 125285.

Protein Science Corporation's questions are presented below followed by CBER responses in bold. Please note that our reviews of BLA 125285 and your response to our IR letter are ongoing and we will provide specific comments on those responses separately.

Process Validation:

1. PSC has submitted three series of drug substance process validation data and/or protocols to the Agency from the period of June, 2007 to the present. Information on drug substance process validation is located in Background Information Section 1 of this package. Does the Agency concur that our August 24, 2009 response to the July 30, 2009 IR is complete and that the drug substance manufacturing process is sufficiently validated for licensure? If not, what additional information is needed?

CBER Response:

We do not consider the process sufficiently validated for licensure at this time. PSC submitted an interim 2009 validation report in July 2009 in response to CBER's request. The Final 2009 Validation report will be needed and is expected to contain the following information:

- a. **Data to support validation of (b)(4) step using a --(b)(4)---- column.**
- b. **Data to support validation of H1 and B HA purification by (b)(4)-- column chromatography**
- c. **Your assay to quantify Tween 20, the associated validation report, and Tween 20 results to support validation of the -----(b)(4)----- step.**
- d. **Data to validate bulk filtration step (performance criteria have not been submitted).**
- e. **To demonstrate the process effectiveness, the -----(b)(4)-----, -----.**
- f. **Data to support consistent purification at the step(s) that increase product purity. The purity attained by the end of (b)(4) is surprisingly low and yet bulk (b)(4) meets specification of (b)(4).**
- g. **Hold time between -----(b)(4)-----, and data to support this hold time.**
- h. **Further data to demonstrate consistency of product quality during the drug substance hold time. This should include records for at least 3 lots of each strain to demonstrate specifications are met throughout the hold time, and demonstration of consistent conditions during the hold time.**

Process parameters or procedures that need to be addressed:

- i. Linear flow rate parameters for the ---(b)(4)--- columns to include a lower limit based on process capabilities.
- j. Testing performed to confirm complete removal of column storage solution prior to use.
- k. Updated acceptance criteria to take into account test variability. For example, when ---(b)(4)--- is a critical process parameter, the variability of the test should be considered in the acceptance criteria.
- l. Documentation of parameters that are visually confirmed when there is no electronic record of conditions used.
- m. -----(b)(4)----- of lot ----(b)(4)----- should have followed SOP QG0041 which states that the lot will be assigned a unique number.
- n. Temperature parameters used for incubation during bioburden tests. If the excursion noted in deviation 09-023 was out of these limits, a rationale for why the temperature excursion was deemed to have minimal impact on the result.
- o. The discrepancy between DNA removal efficiency in Process Development and full scale manufacture.
- p. Results of ----(b)(4)---and -----(b)(4)----- for -----(b)(4)----- samples (one lot each of H1, H3 and B HAs) -----(b)(4)----- analysis in order evaluate the presence of -----(b)(4)-----.
- q. Validation of your ----(b)(4)----- DNA assay.
- r. We agree that quantitative analysis for -----(b)(4)----- is unnecessary; however, it should be listed as a potential impurity.
- s. Specification for Triton X-100 (based on results from the 2008 season, not 2007).
- t. -----(b)(4)----- should be included as an upper limit for drug substance specification.

Concerning -----(b)(4)-----:

- u. Lack of documentation to support your claim that the Quality Unit knew of and approved the -----(b)(4)----- step associated with Process Validation Lot ----(b)(4)--- prior to its execution on May 4, 2009.

Concerning Formulation and Filling:

- v. Microbial failure occurs in the leak rate region of $10^{-4.5}$ to 10^{-3} std cc/sec, which roughly corresponds to leak diameters ranging from 0.4 to 2 microns. It is not clear if your method can detect a critical leak in the range mention above.
- w. Container closure integrity validation must be repeated with vials used in the shipping validation study or repeat container closure integrity testing to include dynamic conditions (i.e., exposure to differential pressures to simulate anticipated product processing or distribution conditions) must be conducted.
- x. Your test plan for confirming reliability of the supplier's results for ----(b)(4)--- for the -----(b)(4)----- stoppers.

2. Given the clinical data from the pivotal studies, including non-inferiority to licensed TIV in two studies and clinical endpoint efficacy results in two other studies, does the Agency agree that the overall clinical results support manufacturing consistency that is adequate to license a seasonal influenza vaccine?

CBER Response:

We are still considering the issue of clinical results supporting the manufacturing consistency and this issue is related to VRBPAC discussion, so we are unable to provide comments on this question.

Product Specifications and Stability:

Information on specifications (product potency, --(b)(4)----, and release) and stability is provided in Background Information Section 2 of this package.

3. Is the Agency in agreement that the information provided supports a minimum potency value of -----(b)(4)----- strain at expiration and a 16 week shelf-life of FluBlok?

CBER Response:

Yes, we agree. Please note that a shelf-life should also be defined for your monovalent bulk drug substance. Please specify shelf-life and provide data to support this length of time.

4. Is the Agency in agreement with a minimum potency of -----(b)(4)-----at the time of drug product release and maximum release potency of -----(b)(4)-----?

CBER Response:

We agree with -----(b)(4)----- as the minimum potency release specification. The maximum release potency of -----(b)(4)----- can also be accepted for the near term. We strongly encourage your commitment to optimize stability in terms of SRID potency to narrow the difference between minimum and maximum potency in each dose.

Formulation and Filling:

5. Information regarding drug product process validation timelines is provided in Section 3 of this package. Pending resolution of product specification matters, we have postponed drug product process validation activities until the end of September/early October timeframe assuming we can reach agreement with the agency on drug product specifications at the September 24, 2009 meeting. Is the Agency in agreement with our proposed timelines?

CBER Response:

Your timeframe appears acceptable. Please submit the data, when available, from two 100% fills prior to licensure.

General

