

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Rakesh Pandey, BLA Committee Chair, OVRR/DVRPA/VVB, HFM-478

From: Deborah Trout, BLA Committee Member, OCBQ/DMPQ, HFM-675

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ, HFM-675

Subject: Review of Biologics License Application (BLA) from Protein Sciences Corporation for the manufacture, formulation, fill and packaging of Recombinant Influenza Vaccine (FluBlok[®]); STN Number 125285/0

My review includes an evaluation of the following sections submitted in Protein Sciences Corporation (reference is made to Comprehensive Table of Contents Module 1): Module 1 (sections 1.1 – 1.3.2 and 1.3.9), Module 2 Quality Summary (sections 2.1. – 2.3.A.1), and Module 3 Quality (sections 3.1 – 3.2.S.2.2.1, 3.2.S.2.2.4 – 3.2.S.2.3, 3.2.3.9 – 3.2.2.5, 3.2.S.3.2 – 3.2.S.4.5, 3.2.S.6 and 3.2.S.7, 3.2.P.1 – 3.2.P.4.4, 3.2.P.5, 3.2.P.5.4 – 3.2.P.5.6, 3.2.P.7 and 3.2.P.8, 3.2.A.1 – 3.2.A.1.2.7, 3.2.R.1 – 3.2.R.1.2.2).

This review memo is divided into 5 main sections followed by page number and date the review was entered into this memorandum:

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**Please note that this review memo is comprehensive with respect to the initial review of the application, the inspection and follow-up review regarding inspectional items. This review memo was finalized July 10, 2009.

Section I: Recommended Action.

Conduct two Pre-license inspections, one for the Bulk Drug Substance and one for the Drug Product. If applicable, waive the pre-license inspection for Drug Product manufacturing at

Hospira. Resolve all issues identified below. Once issues are resolved and all facility pre-license inspections are closed out, I will prepare an approval recommendation memo.

Section II: Filing Issues that can be addressed in the STN assignment letter (Review Date: 05/14/08).

1. Please provide a comprehensive list of all additional products that are manufactured or manipulated in the same areas used to produce the drug substance and drug product. Information provided should include a brief description of the type and developmental status of the additional drug substances/products and indicate the areas into which these other products will be introduced.
2. Please provide a description of how product-contact equipment used to produce the drug substance and drug product is cleaned. In addition, please provide a summary of the validation data to support cleaning procedures.
3. Please provide a validation summary for WFI system at your Protein Sciences facility. The validation summary should include the following information:
 - a narrative of the validation process including acceptance criteria;
 - parameters monitored and tests performed; and
 - explanation of all excursions or failures.
4. Please provide a comprehensive list of all computer systems which control critical manufacturing processes for the drug substance and drug product. Please include a validation summary for each of these systems.
5. Please provide a description of the sterilization and depyrogenation processes used for drug product final containers, closures, and equipment. A description of the validation of these processes should be provided including, where applicable, heat distribution and penetration summaries, biological challenge studies and routine monitoring procedures.

Section III: Outstanding Issues that can be addressed in an Information Request, Deficiencies or Complete Response letter (Review Date: 8/13/08).

1. Please be advised that, based upon our review thus far, we do not concur with your assessment that the manufacturing process for the monovalent bulk drug substances has been validated at commercial scale. Identification of critical quality attributes and control of these attributes through the establishment of appropriate critical control parameters appears inadequate. Your process validation studies do not provide sufficient evidence of control of the critical quality parameters associated with the critical quality attributes. We recommend you review your process and consider additional parameters for testing.
2. We note from Section 3.2.S.2.5 "Process Validation" that the following manufacturing -

steps were not included in your process validation assessment: -----
----- (b)(4) -----

----- . Please provide a revised process validation protocol(s) and associated data for the manufacturing steps mentioned above. Please note that a Process Validation Protocol is a written plan pre-approved by the quality unit that specifies critical steps, controls, and measurements. The Process Validation Protocol states how validation will be conducted, identifying sampling, assays, specific acceptance criteria, production equipment, and operating ranges. Results obtained for each study described in the protocol should be evaluated in an associated process validation report.

3. You indicate in Section 3.2.S.2.5 “Process Validation” that validation will be executed on the H3 component of the vaccine produced in 2008. Please submit the Process Validation Protocol and associated data for the H3 component.
4. You indicate in Section 3.2.S.2.5 “Process Validation” that performance of the (b)(4) Chromatography Step was evaluated by monitoring --- (b)(4) ----- of product load. Please explain how these two parameters adequately assess capture and purification of the rHA protein. In addition, please provide information and results that support control of process contaminants; product purity; yield; cleaning; sanitization; and storage for the (b)(4) Chromatography Step. If small scale studies were performed to assess these items please provide the validation protocols and associated data. In addition, please explain how full scale studies were evaluated to confirm scaled down lifetime studies.
5. Process Validation Lot -- (b)(4) --- Wisconsin/H3 was ----- (b)(4) ----- due to --- (b)(4) ----- . Please include validation of this step in your revised process validation plan.
6. You indicate that Batch analyses from Drug Product Process Validation runs #2 and #3 produced at your contract manufacturer will be submitted as an amendment to the BLA in August. Please provide validation summaries for runs #2 and #3. The validation summary should include the following information:
 - a narrative of the validation process including acceptance criteria;
 - parameters monitored and tests performed; and
 - explanation of all excursions or failures.
7. You indicate that filter and maximum product hold time validation studies will be completed prior to commercial distribution and that results will be submitted to the BLA with the data from process validation runs #2 and #3 in August 2008. Please submit these data
8. Please clarify if container closures were exposed to differential pressures during integrity testing to simulate anticipated product processing or distribution conditions.

9. Please provide information regarding any confirmatory testing performed at your contract manufacturer Hospira, Inc. for data reported in the Certificate of Analysis for the ---(b)(4)----- Stoppers. Please note that Hospira may rely on a supplier's Certificate of Analysis for release of the ---(b)(4)----- stoppers provided that Hospira periodically performs their own testing and the results are consistent with the supplier's data. Once that reliability is established, then the level of testing by Hospira may be reduced.
10. Outstanding inspectional issues identified on the FDA Form 483 dated July 11, 2008 issued at the conclusion of the pre-license inspection of your Meriden, Connecticut location have yet to be resolved. You must satisfactorily resolve these issues prior to approval of the application.

Section IV: Pre-license Inspection Issues

Protein Science Corp., (PSC) Facility Issues (Review Date: 07/03/08)

1. The BLA indicates that purity of ----(b)(4)----- were affected by scale-up, implementation of the universal purification strategy, and improvement in the sensitivity of the purity assay. Pre-validation studies of the purity assay indicate that the assay had a limit of quantitation that did not allow an assessment of ---(b)(4)--- purity. A more sensitive assay was developed with a lower limit of quantitation. Consequently the previously used specification of ---(b)(4)--- was modified to the current specification --(b)(4). During the pre-license inspection please determine if any retain samples are available from batches tested prior to implementation of the more sensitive assay to confirm the justification for the -(b)(4)- purity specification.
2. PSC indicates in their June 13, 2008 response that they do not produce WFI, but purchase it from -----(b)(4)-----, Full USP testing is performed for selected lots (every (b)(4) lots from qualified vendors or every lot from a non-qualified vendors) and identify testing for remain lots. Qualification requires testing of 3 consecutive lots. All buffers are prepared with at least USP purified water (PUW), while USP WFI is used at process step ----- (b)(4)----- and ----(b)(4)-----, WFI is not used to clean any product contact equipment. During the pre-license inspection please follow-up on any product contamination events that may be associated with the use of PUW. Please review one year of water monitoring data for PUW points of use servicing the facility. Please note that WFI is distinguished from PUW by its defined endotoxin level of ≤ 0.25 EU/mL, and its microbial level. WFI is 10 CFU/100mL and PUW is 100 CFU/mL. FDA recommends the use of WFI as early as is possible in the production of parenteral products. It's also recommended that WFI be used for formulation of culture media and purification buffers, and for final steps of drug substance processes, and final rinse of product contact equipment.

3. Bioburden is sampled at steps ---(b)(4)----- and after ---(b)(4)---- on the ----(b)(4)-----
----- (release test).

[(b)(4)]

Sporadic elevated bioburden results were reported in 2007 and earlier in 2008. During the pre-license inspection please review the investigation(s) associated with the sporadic elevated bioburden results reported in 2007 and earlier in 2008. The investigation(s) should take into account the use of PUW in the manufacturing process and for the cleaning of product contact equipment.

4. During the pre-license inspection please review changeover procedures used between manufacturing campaigns for different products. PCS indicates in their June 13, 2008 response that in addition to the production of FluBlok, PSC manufactures -----(b)(4)---
-----.

Comprehensive Drug Substance List			
Product Name	Strain	Year	Purpose
FluBlok	H3/Brisbane	2008	Commercial
FluBlok	B/Florida	2008	Commercial
(b)(4)			
FluBlok	B/Malaysia	2008/2007	Phase III Clinical/Validation
(b)(4)			
FluBlok	H1/Solomon Islands	2007	Phase III Clinical/Validation
FluBlok	H3/Wisconsin	2007	Phase III Clinical/Validation
FluBlok	B/Ohio	2007	Engineering
FluBlok	H1/New Caledonia	2007	Engineering

5. Please review the following regarding equipment cleaning of the -----(b)(4)-----
-----,; The frequency of routine or periodic testing following the cleaning procedure, sampling procedure, residual detergent detection, and frequency of revalidation. If the cleaning procedure is manual, the firm should have validation demonstrating reproducibility and routine testing to ensure validated process is maintained. In addition, residual limits and acceptance criteria should be achievable and verifiable. The manufacture should be able to document by means of data that the level of residuals and acceptance criteria are scientifically sound.
6. In 2003 and 2004 the Process Development group focused on the development of a universal manufacturing process that could be applied to rHAs from a wide range of influenza viruses as recommended by the FDA. During the pre-license inspection please review the universal purification process. PCS indicates that the universal process also had some disadvantages including a reduced overall process recovery and rHA purity compared to previously produced batches. The application indicates that drug products manufactured during implementation and refinement of the universal purification process have been investigated in clinical studies PSC01, PSC02, and PSC03. The process used to manufacture drug product in 2007 for studies PSC04 and PSC06 is essentially the commercial process that will be used to manufacture the 2008 launch lots using the 2008-2009 seasonal influenza formulation.
7. Please review validation associated with cleaning and storage of the ---(b)(4)-----
columns ---(b)(4)--- used to purify the rHA proteins.
8. Please review process validation associated with the -----(b)(4)----- The -----
----- (b)(4) -----
-----.
9. Please review process validation for the --- (b)(4) ----- process, performed by ----(b)(4)---

----- (b)(4) ----- . This operation -----

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

- 10 Protein Sciences implements a raw materials and vendor management program for product launch that uses a patient risk-based approach. Raw materials containing the highest risk (i.e., ----- (b)(4) -----) will undergo the most extensive testing and be under the tightest control. During the pre-license inspection please review their vendor qualification program for critical components.
11. The Bulk Drug Substance is -----
----- (b)(4) ----- . Please review
----- (b)(4) ----- data and (b)(4) validation associated with the --- (b)(4) ----- during the pre-license inspection.
12. During the pre-license inspection please verify how purification column matrices are stored between uses and cleaned and sanitized prior to re-use. Please verify that ----- (b)(4) ----- are monitored for every column run to ensure storage conditions and storage buffer routinely maintain a bacteriostatic effect.
13. Please review (re)validation of the ----- (b)(4) ----- and associated transfer lines.
14. Please confirm during the pre-license inspection that all in-process bioburden samples are taken prior ----- (b)(4) -----.

Hospira Facility Issues (Review Date: 7/3/08)

If applicable, waive the pre-license inspection for Drug Product formulation and filling at Hospira.

15. During the pre-license inspection, the following items should be evaluated: revalidation of the HVAC system; HEPA filter certification and tests performed for the renovated filling suite. In addition, please review environmental monitoring for both viable and non-viable particulates; monitoring of differential pressures, air temperatures, and humidity for both aseptic filling suites.
16. Please confirm that fluid pathways such as tubing are compatible with the Drug Product (i.e., do not absorb in-process materials, and do not leach unintended substances into in-process materials or the Drug Product).

12 Pages determined to be not releasable: b(4)

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

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

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

Drug Product

The complete names, addresses, and responsibilities of the facilities for the manufacturing, release and stability testing of FluBlok[®], are listed in **Error! Reference source not found.** below.

Facilities for the Drug Product Manufacturing, Testing and Stability Testing

Company Name and Address	Contact Name	Responsibilities
Hospira, Inc. 1776 N. Centennial Drive McPherson, KS 67460 Registration No. 1925262	Daniel Proctor Manager, Plant Quality Assurance (620) 241-6200, Ext. 6189 Fax (620) 241-6284 dan.proctor@hospira.com	- -----(b)(4)----- ----- - -----(b)(4)----- - -----(b)(4)----- ----- - -----(b)(4)----- - -----(b)(4)----- ----- - -----(b)(4)----- ----- - -----(b)(4)----- ----- - -----(b)(4)----- -----
Protein Sciences Corp. 1000 Research Parkway Meriden, CT 06450-7159	Mark Michalik Vice President, Operations (203) 686-0800 ext 319 Fax (203) 686-0268	- -----(b)(4)----- - -----(b)(4)----- ----- - -----(b)(4)----- -----

(b)(4)

(b)(4)

(b)(4)

The final formulation of FluBlok (e.g., for the 2007-2008 season) is (per 0.5 mL dose):

- 45µg rHA A/Solomon Islands/3/2006 (H1N1)
- 45µg rHA A/Wisconsin/67/2005 (H3N2)
- 45µg rHA B/Malaysia/2506/2004
- Sodium phosphate, 10-20 mM
- Sodium chloride, 150 mM
- Polysorbate 20 (Tween 20), 0.005%
- Water for Injection (WFI)
- ----(b)(4)-----

(b)(4)

8 Pages determined to be not releasable: b(4)

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

[(b)(4)]

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

[(b)(4)]

Media fill data reviewed appeared acceptable.

Process Validation for Drug Product

PSC and the FDA agreed to a process validation approach of a (b)(4) scale run (b)(4) of formulated trivalent bulk) in Q4 2007 (to be submitted in the BLA) and one (b)(4) scale run and one 100% scale run (to be submitted as an amendment to the BLA in August 2008) at the pre-BLA meeting on September 21, 2007. The maximum batch size (100% scale run) will be (b)(4). PSC may decide to increase the second (b)(4) scale run to a 100% scale run for reproducibility at the full commercial scale.

Batch analyses for the lots produced for the 2008/2009 season will be submitted as an amendment to the BLA in August.