

Memorandum

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

To: File STN: 125285/0/13

From: Deborah Trout, Committee Member, MRB1, DMPQ, OCBQ, HFM-675

Through: Carolyn Renshaw, Branch Chief, MRB1, DMPQ, OCBQ, HFM-675

Subject: Review of CR letter responses submitted April 27, 2009 by Protein Sciences Corporation (hereafter referred to as PSC).

Action Due Date: June 3, 2008

Recommendation: Outstanding issues identified below can be addressed in an Information Request, Deficiencies or Incomplete Response Letter.

CR letter comment 1a:

The data provided are insufficient to assess consistency of the manufacturing process. Please provide tabulated results of critical process parameters and in process tests of product yield for each manufacturing step for H1, H3 and B monovalent bulk lots prepared in 2007 and 2008.

Review of response 1a:

The firm has provided the requested information.

PSC indicates that based on their 2008 campaign the manufacturing process is consistent. I disagree with their conclusion. PSC has failed to address the overall lack of consistent manufacturing. As noted below approximately 50% of the lots manufactured in 2008 were terminated. I did not review the 2007 manufacturing campaign.

2008 Process Validation lots are highlight in blue

----- (b)(4) -----	
----- (b)(4) -----	Zero yield (terminated lot)
----- (b)(4) -----	Zero yield (terminated lot)
----- (b)(4) -----	Zero yield (terminated lot)
----- (b)(4) -----	Zero yield (terminated lot)

----- (b)(4) -----	
----- (b)(4) -----	
----- (b)(4) -----	Reworked lot
----- (b)(4) -----	
----- (b)(4) -----	Failed tech transfer (terminated lot)
----- (b)(4) -----	
----- (b)(4) -----	
----- (b)(4) -----	Equipment failure (terminated lot)
----- (b)(4) -----	----- (b)(4) ----- and irregular column performance (terminated lot)
----- (b)(4) -----	
----- (b)(4) -----	
----- (b)(4) -----	
----- (b)(4) -----	
----- (b)(4) -----	Cracked column (terminated lot)
----- (b)(4) -----	----- (b)(4) ----- breach (terminated lot)

Comment to be relayed to the firm:

- We note from the 2008 manufacturing campaign that approximately 50% of lots were terminated. Please comment on how you are addressing manufacturing consistency for the 2009 campaign.

CR letter comment 1b:

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.

Review of response 1b:

The firm’s response is not complete. PSC has submitted an unexecuted 2009 Process Validation Protocol for review (Attachment 3). The protocol has been updated to include the following manufacturing steps: ----- (b)(4) ----- .

Comments to be conveyed to the firm:

- Concerning ----(b)(4)---- chromatography 2009 process validation; you did not describe in-process testing and acceptance criteria to assess purity during these chromatography steps. Please clarify how you will reproducibly demonstrate the reduction of impurities to desired levels during these manufacturing steps.
- Concerning ----(b)(4)----- 2009 process validation; we note there is no acceptance criteria set for DNA removal for this manufacturing step. Please clarify how you will reproducibly demonstrate DNA removal to desired levels during this processing step.
- Please provide the data and associated summary report for the 2009 process validation protocol.

CR letter comment 1c:

Review of your process shows that downstream steps use strain-dependent conditions and therefore we request that you demonstrate consistent manufacture as measured by yield and quality in three consecutive H1, H3 and B batches that meet all specifications. The Process Validation study presented in the BLA does include 3 lots of B rHA that performed consistently in clinical trials. Please provide evidence that these lots were generated as consecutive batches, and submit in-process test results to demonstrate process consistency at each step in addition to yield and quality (----(b)(4)-----) of each monovalent bulk.

Review of response 1c:

The firm's response is unacceptable.

Concerning the H3 Process Validation Report R-09-005 for the 2008 manufacturing campaign: PSC states that three consecutive runs for the H3 strain were completed and that the H3 process is validated.

The batches listed below in **bold** were used to complete the 2008, H3 process validation study.

Lot#	Deviation(s)	Disposition
----(b)(4)-----	Manufactured before the validation protocol was written	Terminated
----(b)(4)-----	No deviations	Acceptable for release
----(b)(4)-----	Bioburden action limit exceeded ----(b)(4)----- (deviation 08-035 and CAPA 08-029)	Acceptable for release
----(b)(4)-----	Equipment Failure	Terminated
----(b)(4)-----	----(b)(4)-----and irregular column performance	Terminated
----(b)(4)-----	No deviation	Acceptable for release

The 2008 validation report fails to mention or take into consideration the failed H1 batch (45-0817) listed above. The process validation should include a justification for why this batch failure (----(b)(4)----- and irregular column performance) would not affect the outcome of the process validation for H3.

The report also states that the ----(b)(4)---- underwent preventative maintenance resulting in the termination of lot ----(b)(4)----- . It is unclear why preventative maintenance would result in the termination of a lot.

Comment to be relayed to the firm:

- Concerning the 2008 Process Validation Report (R-09-005) for H3: we note that an H1 batch (---(b)(4)--- was manufactured in between your process validation runs for H3. The H1 batch (----(b)(4)-----) was terminated for ----(b)(4)-----and irregular column performance. Please provide a justification for not assessing the impact of this deviation on the H3 process validation study.

CR letter comment 2g:

Re-use of columns: If columns will be used multiple times please provide lifetime studies to support reuse, cleaning, sanitization and storage. 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.

Review of response 2g:

The firm's response is not complete.

Comments to be conveyed to the firm:

- It is unclear if your lifetime studies for the ----(b)(4)----- columns included an evaluation of protein load capacity and linear flow rate. Please clarify. If these parameters were not assessed please provide a justification for not including them in the study.
- It is unclear if cleaning, sanitization and storage procedures used in your scaled-down study for the ----(b)(4)----- columns are the same procedures that are used in your commercial scale purification process. Please clarify
- We note you only assessed ----(b)(4)----- in your lifetime studies to support cleaning and sanitization of the ----(b)(4)----- columns. Please provide a justification for not including other parameters such as -----(b)(4)----- in your assessment of cleaning and sanitization.

CR letter comment 2h:

Concerning the ----(b)(4)-----: Please provide information on any preconditioning, cleaning, and sanitization or sterilization performed.

Review of response 2h:

The firm's response appears acceptable.

PSC is pre-conditioning according to (b)(4) recommendations. The ----(b)(4)---is sanitized with

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CR letter comment 11a:

Please submit information on how monovalent bulk drug substance is shipped to and stored at Hospira.

Review of response 11a:

The firm's response is not complete.

The monovalent bulk concentrates are shipped in qualified shipping containers from -(b)(4)-. The container is qualified for (b)(4) shipments. Upon receipt at Hospira a visual inspection of the container is performed. All containers are verified for identity of the drug substance, lot number, and quantity. It is unclear if an identity test is performed on the monovalent bulk concentrates when it is received at Hospira or if the firm is relying on a Certificate of Analysis to confirm identity.

Comment to be relayed to the firm:

- It is unclear if an identity test is performed as per 21 CFR 211.84(d)(1) on the monovalent bulk concentrates when they are received at Hospira. Please clarify.

CR letter comment 11d:

Please provide Drug Product Process Validation summaries for runs #2 and #3. The validation summary should include a narrative of the validation process including acceptance criteria, parameters monitored and tests performed, and explanations of all excursions or failures.

Review of response 11d:

The firm's response is not complete.

To date PSC has completed one (b)(4) batch size (Run 1) and a (b)(4) batch size (Run 2). A validation protocol was generated in 2008 for Run 2. PSC provided fill uniformity data for potency and pH for Run 2. PSC will complete Run 3 in July 2009 with the data available at the end of August 2009. There was one deviation associated the Run 2, a low fill volume was identified during final release testing. Corrective action will be to increase the target fill volume in the batch record.

Comments to be conveyed to the firm:

- Please provide validation data in support of fill volume accuracy for the ----(b)(4)-----.
- Please provide the data and associated summary report for Drug Product Validation Run #3.

CR letter comment 11e:

You indicate that filter and maximum product hold time validation studies will be completed prior to commercial distribution. Please submit these data.

Review of response 11e:

The firm's response is not complete.

Data was provided for a --(b)(4)-- hold which was defined as the -----(b)(4)-----
----- Testing included -----(b)(4)----- (b)(4)----data was not
included in the summary report for the -----(b)(4)-----time points.

Comment to be relayed to the firm:

- Concerning the formulation hold study, please provide --(b)(4)- - testing results for the ---
---(b)(4)----- time points.

CR letter comment 11f:

Please clarify if container closures were exposed to differential pressures during integrity testing to simulate anticipated product processing or distribution conditions.

Review of response 11f:

The firm's response is unacceptable.

PSC indicates that media filled units were sealed at the maximum and minimum sealing pressures to simulate worst case production parameters.

Comments to be relayed to the firm:

- Please provide a corresponding leak rate or leak diameter for your positive control vial used in the container closure integrity test study.
- Please explain how minimum seal pressure would simulate pressure differentials experienced during (b)(4) transportation of your container closure system.

CR letter comment 11g:

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. Please provide information regarding any confirmatory testing performed at Hospira for data reported in the Certificate of Analysis for the ----(b)(4)---- Stoppers.

Review of response 11g:

The firm's response is unacceptable.

PSC indicates that release testing for ----(b)(4)-- is based on the supplier's Certificate of Analysis and reliability has been established through supplier inspection and approval, confirmatory testing was deemed unnecessary by Hospira.

Comment to be relayed to the firm:

- Your response is unacceptable. Please provide test data, from Hospira, confirming reliability of the supplier's results for --- (b)(4)--- for the ----(b)(4)---- stoppers.

CR letter comment 12:

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.

Review of response 12:

This issue will be covered under a separate review memo.