



Memorandum

DATE: 15 January, 2013

FROM: Maryna Eichelberger, Ph.D.

THRU: Jerry Weir, Ph.D.

CC: Anissa Cheung, M.S.

SUBJECT: BLA STN 125285, CMC review

PRODUCT: Flublok, influenza vaccine

SPONSOR: Protein Sciences Corporation

Review of the Chemistry, Manufacturing and Control Information Relevant for the drug substance (monovalent bulk rHA for H1, H3 and B strains) and drug product (trivalent formulation) submitted in the BLA application STN 125285 from Protein Science Corporation

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This BLA application from Protein Sciences Corporation (PSC) is for licensure of baculovirus-expressed insect cell-derived recombinant hemagglutinin (rHA), under the trade name Flublok. The vaccine is a mixture of purified recombinant hemagglutinins derived from H1, H3 and B influenza viruses recommended for seasonal influenza vaccine production. This trivalent product is a sterile solution with no added preservatives for intramuscular immunization. Each 0.5 ml dose contains 135 µg (45 ug of each strain) rHA and will be for active immunization of adults 18 - 49 yrs. This review focuses on the Chemistry, Manufacturing, and Control information for the drug substance (monovalent bulk rHA for H1, H3 and B strains) and drug product (trivalent formulation) submitted in the original BLA application received on 17 April, 2008 and associated amendments, in addition to responses to CR letters issued 29 August 2008 and 11 January 2010, and associated amendments.

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Reviewer comments: I am satisfied with PSC’s responses to the comments concerning process parameters, and concur with the changes they have made to improve process robustness. Data from downstream process steps of H1, H3 and B (3 lots each) were submitted to support validation of these steps for each strain. I have reviewed these data and concur that they demonstrate consistency of the downstream manufacturing process.

2. Changes in the manufacturing process

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- Annual strain change: Conditions need to be optimized to support production of rHA from new strains recommended for vaccine production. -----
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----- . A list of updated conditions is provided for review in the strain change supplement. I concur with this approach to optimize production.
- Changes in the manufacturing process since pivotal clinical trials: Drug Product used in clinical trial PSC04 in 2007 was manufactured prior to process validation. Although manufactured at a different scale, the approach and consumables were the same except for the ----(b)(4)----- step. Process improvements that were introduced did not result in qualitative differences in Drug Product.

Reviewer comments: The changes that have been made to the process since 2007 do not have a negative impact on product quality (including purity and potency), and therefore data collected in pivotal trials are valid. I concur with the use of unique conditions for the H1, H3 and B downstream process and agree with optimization of these conditions for strain change.

3. Formulation and fill

There were problems with initial formulation and fill steps conducted by Hospira. The following procedures have been put in place to ensure successful formulation and fill:

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Resolution: After extensive exchange of information (details in section 5), PSC provided rHA to CBER that was lyophilized and calibrated for use as a reference antigen. Both CBER and PSC are monitoring stability of the reference so that fresh reference material can be prepared as soon as it is needed.

Reviewer comments: PSC plans to use CBER-approved SRID reagents and is aware that CBER prefers a conservative approach, requiring extensive characterization of reference antigens and antisera if the usual reference reagents are not suitable. To be prepared for a manufacturing campaign, PSC has initiated SRID reagent qualification testing. PSC will include data from the SRID reagent qualification testing in strain change supplements so that CBER can evaluate these results and provide guidance if necessary.

6. PSC04 lot consistency trial

The manufacturing process had not been validated prior to pivotal clinical consistency trials, including PSC04. In 2007, 3 drug product lots, 50-07010 (Lot A), 50-07011 (Lot B) and 50-07014 (Lot C), each formulated with different monovalent bulk lots, were tested in clinical study PSC04 to evaluate clinical lot consistency. Each drug product batch was formulated to contain 45µg of each antigen as determined by SRID. HAI titers to H1 and B components for individuals vaccinated with different lots were similar, but HAI titers to the H3 (A/Wisconsin/05) component of Flublok Lots B and C were significantly lower than the titers following vaccination with Lot A. Despite this, CBER immune response criteria were met for all three lots. The lower immunogenicity was due to inaccuracy of SRID potency measurements – the H3 monovalent bulks used to formulate Lots B and C had ----(b)(4)----- . Formulation based on SRID values therefore resulted in these lots not containing as much H3 as Lot A which was formulated with a monovalent bulk that had a ----(b)(4)----- .

Resolution: A DS specification for ----(b)(4)----- has been added, together with procedures to -----(b)(4)----- . As a result every Flublok vaccine will contain at least 45 µg HA protein/dose.

Reviewer comments: Clinical consistency was demonstrated for H1 and B components of 3 vaccine lots used in PSC04. I am confident that the root cause of the difference in H3 HAI titers was formulation based on SRID values that were inaccurate for 2 lots with -----(b)(4)----- . In my opinion, since this inaccuracy of potency measurement is now controlled, and there is provision to formulate vaccine with no less than 45 µg HA protein/dose, it is not necessary to verify consistency of the H3 component in clinical studies.

REVIEWER'S RECOMMENDATION:

PSC has provided data demonstrating consistent production of Drug Substance (monovalent bulk) and trivalent Drug Product, has appropriate specifications for intermediates and Drug Product that are tested in validated assays, is using a validated SRID assay to measure potency with results comparable to those measured at CBER, has sufficiently characterized their product and its stability, and has appropriately addressed inspectional concerns. Based on the CMC data submitted, I recommend approval of PSC's license application for Flublok influenza vaccine, with a shelf-life of 16 weeks.

CMC Review

1. Manufacture sites and contract laboratories

Protein Sciences Corp., Meriden, CT: At this site, rHA monovalent bulk concentrates (drug substance) are manufactured; release tests and stability tests of drug substance are performed; small scale formulation of drug product, potency, DNA content and stability tests of drug product are performed.

Hospira, McPherson, Kansas: At this site, the drug product is formulated, filled, packaged and labeled. Container closure tests and release tests are performed (with exception of potency and DNA quantitation) at Hospira.

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2. Manufacturing materials and the manufacturing process

2.1 General information

The purified recombinant influenza hemagglutinin (rHA) drug substances included in the Flublok drug product are derived from strains representing influenza A subtypes H1N1 and H3N2 and influenza B. The rHA genes are cloned from the strains approved by FDA on an annual basis. The selected viruses are obtained from CDC and then the full-length HA gene is cloned into the baculovirus *Autographa californica* nuclear polyhedrosis virus (AcNPV). PSC has developed the expresSF+ cell line, which can be propagated in a serum-free medium, as the substrate for recombinant baculovirus infection and rHA production. This is a non-transformed, non-tumorigenic, continuous cell line derived from the fall army worm, *Spodoptera frugiperda*.

Based on PSC's experience with rHA substances of several influenza strains, the monovalent bulk proteins are (b)(4)---, and the purified rHA's migrate on SDS-PAGE -----
----- (b)(4) ----- with molecular weights of about 65 kDa, -----

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

----- By electron microscopy, rosette-like micelle structures are observed. Purified rHA can agglutinate avian red blood cells, which indicates its ability to recognize sialic acid receptors as well as its higher order association into rosettes.

Potency of the vaccine is measured by single radial immunodiffusion (SRID) assay. This assay uses CBER-approved reference antigen and HA-specific sheep antisera that are used to measure the potency of US licensed trivalent inactivated influenza vaccines. However, in instances when these reagents are not suitable, recombinant HA has been prepared and qualified for use in the assay as described in section 5 of this review.

2.2 Raw materials

PSC implements a raw materials and vendor management program in which raw materials containing the highest risk (final formulation components) are under the tightest control (most extensive testing). Each raw material has been assigned a PSC-part number (A through F) to allow for segregation upon receipt.

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Reviewer comment: PSC has a suitable raw material management program and has demonstrated extremely low risk of introducing infectious agents in materials of animal origin. I have no concerns regarding raw materials used for production of Flublok.

2.3 Cell banks

Cell banks were reviewed by an expert in cell substrates, and therefore cell bank characterization is described in a separate review.

2.4 Master Virus Bank (MVB)

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**Reviewer comment: The tests performed show that known adventitious agents are not present in the master virus bank, -----(b)(4)-----
-----, This MVB is suitable for production of WVB.**

2.5 Working virus banks (WVB)

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2.6 Manufacturing process

2.6.1 Process development. In PSC's original application submitted 17 April 2008, the sponsor explains that initial clinical studies of FluBlok were conducted under a series of three Investigational New Drug Applications (INDs) sponsored by the Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), beginning in 1993, using monovalent or bivalent rHA vaccine formulations manufactured by Protein Sciences Corporation (PSC) for NIAID. Under the NIAID INDs, a number of Phase 1/2 safety, immunogenicity, and dose-ranging studies were conducted. A description of the steps used to purify rHA used for these studies is included in section 3.2.S.2.3 of the original BLA submission. In this section they also describe investigation of various methods for optimizing separation of the rHA proteins from the baculovirus vector and from insect cell proteins, and to remove contaminating baculovirus and host cell DNA. In 2004 PSC developed a "universal" process for purification of the rHAs from all influenza strains that would be included in a trivalent formulation of a seasonal influenza vaccine and this process has been used for clinical studies of Flublok under PSC's own IND, BB-IND 11951, starting with clinical Study PSC01. Under this IND, further refinements of the purification scheme and scale-up production of the rHA drug substance were accomplished to increase production capacity and process robustness. However, the manufacturing process was not validated or completely characterized and optimized prior to the pivotal clinical efficacy trial in young adults (PSC04). Indeed, lack of clinical consistency of the H3 component in this trial and failure to manufacture HA from all 3 strains consistently required significant improvement of the manufacturing process. Only minor adjustments to the universal process are needed to support the purification of new rHAs recommended as strain changes.

Reviewer comment: The process used by PSC to prepare vaccine used in INDs under the auspices of NIH were significantly different from the universal process used in clinical trials under IND 11951. In my opinion, because these differences could impact product safety and immunogenicity, the data from NIH-sponsored studies should not be used in conjunction with evaluation of product used in PSC-sponsored studies. The manufacturing improvements made since PSC-sponsored clinical studies conducted in 2007 have no negative impact on product safety and efficacy. These improvements have resulted in greater process robustness and increased consistency of product quality.

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Reviewer conclusion: the USP and DSP steps are sufficiently characterized to allow consistent product yield and potency. Validation of these steps is discussed in section 3 of this review.

2.6.3 Process steps conducted at Hospira. The trivalent drug product is formulated and filled at Hospira (McPherson, Kansas). The original BLA submission did not include sufficient information regarding formulation and fill process, and initial fill runs were unsuccessful. As a result the steps conducted to ensure drug product specifications will be met have been clearly defined in SOP

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Single glass vials are used -----(b)(4)----- with elastomeric closures -----(b)(4)----- and crimp sealed (aluminum with tear-off center seal). The ---(b)(4)--- stoppers do not contain dry natural rubber and therefore have low potential of causing allergic reactions in individuals with latex allergies. Studies have been done to demonstrate compatibility of these components with the drug product. CBER has agreed that Hospira can 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. CBER also advised that Hospira testing can be reduced once reliability of the CoA is established. Container closure validation was performed at Hospira. These data were reviewed by OCBQ.

Single dose vials are then labeled and packaged, and sent to PSC by truck at 2-8 °C. Potency assays and testing for DNA concentration is conducted on filled vials at PSC ----(b)(4)----- . PSC also performs drug product stability tests. Hospira is responsible for testing excipients and components (vials, stoppers, seals), blending, filling, release testing of the drug product (excluding potency and DNA content), packaging and labeling of the drug product. CBER conducts lot release testing on filled vials.

Qualification tests performed on the final filled containers include: appearance, sterility, potency/identity, fill volume, endotoxin, and the general safety test.

Reviewer comment: While the original submission received on 17 April 2008, lacked information to support the formulation and fill process, data provided in amendment 55 (27 March 2012) demonstrated that this process is consistent (see process validation below) showing that procedures have been put in place to achieve targeted potencies of H1, H3 and B components in the filled, trivalent product.

3. Process validation

3.1 Validation of process steps performed at PSC: The data presented in the original BLA (18 April 2008) did not provide data demonstrating consistency of the manufacturing process (upstream, downstream as well as formulation and fill) and therefore this was a major comment in the CR letter of 28 August 2008. In addition, the 483 issued during the PAI conducted in July 2008 noted process failures that had not been appropriately investigated (comment 3 of the 483 form issued 7/11/2008), raising further concerns about the oversight and control of process steps. CBER asked for evidence that problems had been resolved (information request July 30th, 2009 comments 1aA and 1aB), the sponsor stated that several steps had been taken to enhance manufacturing consistency as a result of 2008 corrective actions. These included changes in planning (a pre-production check to ensure all required materials are in place), process transfer (SOP RG0006 DSP Process Development of New rHA strains" has been implemented), ----b(4)-----

The 2009 validation protocols P-09-012 (upstream validation protocol) and P-09-013 (downstream process validation protocol) were included as attachments 2 and 3 in the April 27, 2009 submission. The upstream protocol specified that ---b(4)-----
----- . For the downstream process, a minimum of 3 consecutive runs were performed for all 3 strains (H1, H3 and B). The process validation was

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Reviewer comments: The following procedures have been put in place to ensure successful formulation and fills:

- **QA0011 “Approval to Formulate Flublok Drug Product”** provides a mechanism to ensure monovalent bulk potency requirements are met prior to shipping material to Hospira
- Potency is measured ----- (b)(4) ----- of formulation to avoid problems due to monovalent bulk instability
- --- (b)(4) --- of the monovalent bulk are tested for potency to give confidence in results used to calculate volumes for blending
- ----- (b)(4) -----

- Drug Product is shipped under controlled conditions back to PSC for release potency testing (3 individual vials); this provides confidence in test results as SRID data generated by Hospira appeared to have greater variability than when tested by PSC

Data from fill runs PV5, PV6 and PV7 have demonstrated consistency of the formulation and fill process. PSC has a protocol in place to monitor stability of product in filled vials from the first 3 lots produced at frequent intervals. Potency, total protein concentration, and ^{b(4)} are measured at --- (b)(4) -----, and sterility is measured --- (b)(4) ----- . All criteria (including potency) were met to the --- (b)(4) --- time for each of these fill validation lots.

Reviewer summary: As demonstrated for 3 validation runs (PV5, PV6 and PV6) performed at full scale (b)(4), the steps the sponsor has put in place provide a way to meet release specifications consistently. I am confident that PSC can manufacture product that consistently meets specifications to expiry.

4. Virus Clearance and adventitious agents

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5. 3. Tests performed ----(b)(4)----- Drug Product include tests for: appearance, identity (determined by SRID – the assay SOP is appropriate and validation shown specificity), purity, host cell protein, endotoxin, bioburden, potency, total protein,-----
----- --(b)(4)----- residual surfactants -Triton X100, --(b)(4)--, Tween-20. -----
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------. In cases where assays are performed both at PSC and Hospira (for example, SRID), the assay was validated at PSC, then transferred to Hospira. Equivalence in test performance was demonstrated through testing the same samples at both sites.

5.3.1. Potency: Potency is measured by the SRID assay (SOP QT0077). This assay is based on CBER's SRID protocol, using CBER approved reference antigens and HA-specific sheep antisera. The assay has been adequately validated at PSC and transferred to Hospira (validation report R-08-006). The potency test has been improved through -----

-----, Stability studies that show loss of potency over time suggest that the SRID assay is an appropriate assay to quantify antigenically-intact rHA, and the CBER reference antigen and sheep antiserum used in the assay provides an appropriate and essential measure of antigenic integrity.

Despite validation, several problems occurred during the course of this application, pointing to a need for vigilant examination of SRID results early in the manufacturing season to ensure the use of the most appropriate reference material:

- SRID values sometimes exceed the absolute amount of rHA in the product. In this case, the SRID assay results are inaccurate because it is not possible to have potency in excess of the absolute amount of rHA. This inaccuracy appears to occur when the assigned reference antigen concentration is less than the actual amount of HA in the reference material. Because the absolute amount of HA is not known in egg-grown vaccine preparations, this is not an issue for other manufacturers, but the discrepancy is easily noted for rHA since total protein concentration is measured by BCA assay. To ensure that the most suitable reference material and antisera are used,

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5.4 Hemagglutination inhibition (HAI) assay: The HAI assay that was used in clinical evaluation of the product is described as ‘standard’: -----

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----- The HAI validation report (revision 28 Feb 2007) from Cincinnati Children's Hospital provided validation parameters that are used to define assay specificity, precision, repeatability, day-to-day variation, analyst-to-analyst variation, robustness -- (b)(4)-----, titer range, and linearity. Each of these parameters was validated for one lot of BEVS-derived HA antigen for each virus type/subtype, using sera samples from either Flublok recipients or unvaccinated controls.

Reviewer comment: In my opinion, it is not necessary to perform complete HAI validation studies for each HA type/subtype. However some comparability studies are useful to understand strain-specific differences when assays are performed with whole virus and recombinant BEVS-derived HA. These differences can impact the interpretation of results: (i) the (b)(4) titer often equated with seroprotection cannot be used since titers using BEVS-derived HA are often significantly greater than assays using whole virus. In any case, this titer has not been established as a correlate of immunity for this novel vaccine which does not contain other influenza antigens that may also contribute to immunity; (ii) seroconversion rates measured using assays that use different sources of antigen (whole virus vs BEVS-derived antigen) are likely to be different due to different sensitivities of each assay. In my opinion, HAI titers and seroconversion rates should not be used on their own to imply vaccine efficacy of Flublok until a HAI titer that correlates with protection of Flublok-vaccinated individuals has been identified. This correlate is likely to be different for adults and children, and therefore future studies to support licensure of Flublok in the pediatric population should include clinical end-points to demonstrate efficacy. This issue has no bearing on the approval of Flublok for persons 18 to 49 yr of age as efficacy was demonstrated in a clinical end-point efficacy trial (PSC04).

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6.2. Drug Product Specifications.

Drug Product specifications that are distinct -----(b)(4)-----:

Total DNA: The specification for total DNA is ≤ 10 ng/trivalent dose. -----

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Table 6. Flublok Drug Product Specifications: at release and through expiry

Test	Method (Reference)	Acceptance Criteria
Appearance	Visual inspection --(b)(4)--	Colorless, clear liquid essentially free of visible particles
Identity	--b(4)--- -----	---b(4)----- -----
Bacterial Endotoxin	----(b)(4)--- ----(b)(4)---	----(b)(4)-----
Sterility	Membrane Filtration (21 CFR 610.12)	No growth observed
Potency at t=0	SRID conducted within ---(b)(4)--- - (QT0077)	-----b(4)----- -
Potency throughout shelf-life	SRID (QT0077)	≥45 µg/dose for each HA component (H1, H3, and B) ----- -(b)(4)----- -----
Purity	-----b(4)-----	(b)(4)
DNA Content	---(b)(4)-- (PSC QT0082)	≤ 10 ng per dose
Total Protein	BCA assay (PSC QT0012)	Mean ₁₀ ≤285 µg/dose
-----(b)(4)----- -----	-----b(4)----- -----	---(b)(4)----
Triton X-100	----(b)(4)--- -----	(b)(4)
----(b)(4)----	---(b)(4)---	-----b(94)-----
(b)(4)	----(b)(4)----- ----(b)(4)----	---(b)(4)---
General Safety	21 CFR 610.11	All animals survive and weigh no less than at time of injection
Fill Volume	--(b)(4)--	Not less than 0.5 mL

Potency: Specifications for Drug Product potency at release and Drug Product potency through the expiry are different because there is significant decay of potency over the 16 week shelf-life. To

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Triton X-100: Triton X-100 -----

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(b)(4)

General safety test: A general safety test is conducted on each drug product lot, with a specification that all animals inoculated will survive and on day 7 post-vaccination not weigh less than the day of vaccination.

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7. Stability

submission. The stability protocol for DS was provided in amendment 66 (16 October 2012). -----

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evidence that all 3 rHA subtypes are more stable in terms of potency when vials are closed with new-style stoppers. However, it should be noted that SRID values at time 0 may be inaccurate as some components had readings 30-50% higher at 1 week than at Day 0.

Stability testing of DP in filled vials was performed on product filled at Hospira in support of fill validation. These data are included in amendment 64 (received 1 October 2012) in which PSC requested extension of Drug Product shelf-life. They provided stability data from each of the 3 drug product fill validation lots: batches --(b)(4)- (PV5), --(b)(4)- (PV6), and --(b)(4)- (PV7) to demonstrate FluBlok specifications (appearance, sterility, b(4), protein concentration, potency) were met out to ---(b)(4)---. PSC requests extension of the shelf life to ---(b)(4)---. In PSC's August 24, 2009 submission, PSC estimated shelf lives for each rHA antigen in the 2007/2008 formulation of FluBlok -----

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----- Based on this analysis, PSC proposed a shelf life of 16 weeks. ----- (b)(4) -----

Reviewer comments: I do not agree that the data submitted support an extension of Flublok shelf-life for several reasons:

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

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9.2. Strain change amendments:

PSC has submitted information to support production of rHA from new strains recommended for manufacture of trivalent influenza vaccines. These amendments include the CoA for the influenza virus from which HA was cloned, information describing the generation of the working virus bank, characterization of the WVB including the HA sequence and its alignment with the reference strain, optimized conditions for manufacture, and antigenic analysis for antigens that are not identical to the reference sequence. PSC has agreed (amendment 66 (16 October 2012)) to including data demonstrating the use of approved potency reagents in SRID assays in future strain change supplements (requested in information request 28 September 2012).

9.2.1. Amendment 34 (10 August 2010): strain change information to include 2 strains, A/California/07/2009 and A/Perth/16/2008, previously not manufactured by PSC for the 2010/2011 vaccine. Since CBER approved reference reagents were not suitable for potency testing, PSC provided well-characterized and freshly prepared rHA to CBER for lyophilization and calibration as described in section 5).

9.2.2. Amendment 53 (27 February 2012): strain change information for 2011/12 vaccine composition. Since serum-free conditions were used at all stages of manufacture, including generation of the WVB, new working virus banks that met all specifications were prepared for each of the 3 strains included in the 2011/12 formulation: A/California/7/2009 (H1N1); A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008.

9.2.3. Amendment 56 (25 June 2012): strain change information to support 2012/2013 vaccine formulation. New working virus banks were prepared for H3 and B components. The genes were cloned from A/Victoria/361/2011 and B/Wisconsin/1/2010, respectively.

Reviewer summary and comments: As for other influenza vaccine manufacturers, submission of strain change supplements is necessary to ensure production of antigen for the recommended vaccine strains. Amendments from PSC to support strain changes have included detailed technical information regarding –(b)(4)----- changes. While these are not essential components of the strain change supplement, the strain change

submission serves as a convenient location to document all supporting information and so we have not discouraged PSC from including this. The essential information needed for review of strain change are: the CoA for the influenza virus from which HA was cloned, information describing the generation of the working virus bank, characterization of the WVB including the HA sequence and its alignment with the reference strain, and antigenic analysis for antigens that are not identical to the reference sequence. We have asked PSC to include data to demonstrate suitability of potency assay reagents (information request 28 September 2012) as during the review cycle we were surprised that PSC did not always approach CBER to resolve potency testing problems. PSC agreed to include this data (amendment 66) to demonstrate reagents are suitably qualified for use in PSC's potency assay. This will give us confidence that CBER reagents are adequate for testing rHA potency of new strains, or will provide the means for us to resolve any problems.

10. Pre-approval inspections

Protein Sciences Corporation manufacturing facility, process development and quality control laboratories were inspected 3 times over the course of this application. Multiple items pertaining to control of the manufacturing process and need for written procedures were identified as 483 items during an inspection in July 2008, inconsistent manufacture of monovalent bulk and need for investigations of deviations were items identified as 483 items during an inspection in October 2009. During a final inspection in November 2012 it was clear that the manufacturing process was controlled and appropriate oversight of the process was in place. All 483 items were appropriately addressed.