



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Date: August 13, 2008

To: Administrative File, **BL STN: 125285/0**

From: Jonathan McInnis, OCBQ, DMPQ, MRB II, HFM-676

Through: Chiang Syin, Ph.D., Branch Chief OCBQ, DMPQ, MRB II, HFM-676

Subject: **Review Memo (BLA):** [Protein Sciences Corporation] Original Biologics License Application for Influenza Virus Vaccine, proposed trade name FluBlok, for intramuscular administration.

Action Due: October 18, 2008

Action Recommended: Based on by review of the materials submitted in the BLA I recommend issuance of a complete response letter requesting the additional information as described in the questions for a complete response letter outlined below.

Questions for a Complete Response:

Upon review of the PSC BLA submission, I note the following omissions:

1. Regarding the facility, there is no detailed description of the changes made as part of the renovations to the facility completed in March. The submission states that the facility is qualified but it is not clear if this refers to qualification completed post-renovation or a prior qualification. Please provide data in support of the qualified status of the facility to include qualification of facility systems including but not limited to HVAC and water. Please provide the following:
 - a. IQ, OQ and PQ for all water systems in the facility following the most recent renovations.
 - b. IQ, OQ and PQ for the HVAC system post renovation.
2. Regarding equipment used in the manufacturing process, please provide operating parameters, such as mixing speeds and flow rates, where applicable as well as the validation protocol followed in determining optimal set points. Please provide the following:
 - a. Performance Qualification of the Decontamination autoclave including the validation plan (i.e. TC placement, number of TCs used) and validation data.
 - b. Performance Qualification of the —b(4)----- including information related to the establishment of mixing speed.

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

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The Single Radial Immunodiffusion (SRID) assay method is an immunological method used to determine hemagglutinin (HA) protein concentration. The test is based on the reaction between HA and a specific HA-antiserum in an agarose gel matrix. HA in the sample well diffuses into the gel containing antiserum and the size of the resulting immuno-precipitation zone is proportional to the amount of loaded HA. The SRID assay has been used to standardize the formulation and antigen content of trivalent inactivated influenza vaccines (TIV) for many years. In dialog with the FDA and to facilitate the comparison between FluBlok and TIV in clinic studies, the SRID assay is also used to assign a potency value to the monovalent bulk batches of recombinant HA used to formulate the trivalent FluBlok vaccine.

The SRID result has been observed to exceed the BCA (total protein) result for rHAs from the H3/Wisconsin and B/Ohio strain. The higher result for B/Ohio is likely explained by a mismatch between the test antigen and the FDA reference standard, which was B/Malaysia. The higher result for A/Wisconsin may be explained by differences in carbohydrates associated with the rHA. Carbohydrates found in avian cells tend to be more complex and as a result the egg-based hemagglutinin may migrate slower in the SRID gel than the rHA.

Clinical Lot Consistency Study Results and Process Comparison

Three drug product lots, 50-07010 (Lot A), 50-07011 (Lot B) and 50-07014 (Lot C), 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 the single radial immunodiffusion method (SRID). The three lots met the pre-defined criteria for A/Solomon Islands and B/Malaysia, but not for A/Wisconsin. As a consequence of the clinical lot consistency failure for H3/Wisconsin, a detailed investigation was undertaken to examine batch records of the three drug substance batches and associated analytical testing in an effort to better understand potential root causes for the failure. Results of this investigation are described below.

Raw Materials

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.

Vendors are also qualified according to a risk-based approach, where those supplying highly critical activities (such as contract production) will be under the tightest control (requiring quality agreements, audits, technical transfer, and change control notification). Raw material category and vendor experience (i.e. – size of company, pharmaceutical delivery experience, and track record) is considered on a per vendor basis when determining what level of control is required.

The purpose of the risk-based approach for raw materials qualification and vendor management/qualification is to introduce a system where attention for critical materials is higher than for less critical material, facilitating efficiency and effectiveness.

The principle behind the Raw Materials Program is:

- The specific use of a raw material (or other materials) in the process or facility determines the designation; that is, how critical that component or material is to the quality of the product. As an example, a head-cover is assigned a designation less critical than an excipient that will be injected into the vaccine recipient.

Each raw material has been assigned a part number that consists of a specific category; A, B, C, D, E, or F and an associated number to allow for segregation of materials. As an example, --b(4)-----

To introduce a comprehensive and operational system, the following has been introduced:

To facilitate the risk-approach and a practical process for both a part-numbering system and the shipping and receiving procedures, a letter-coding designation was defined:

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Facilities and Equipment

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All areas of the manufacturing plant are environmentally controlled as necessary to provide protection from contamination by dust or other foreign materials and to provide controlled temperature conditions. Heating, ventilating, and air conditioning requirements are met by a series of separate systems serving specific areas. Air pressure differentials are utilized to assist in preventing airborne contamination. Plant services such as domestic water, power, heat, and light are available throughout the facility. Special services such as compressed gases, clean steam, and purified water are provided as required to the production areas. All systems are controlled to prevent cross contamination.

The facility is designed to promote essentially uni-directional product flow from the receiving area in --b(4)-- -----

Access to the manufacturing facility is limited to authorized personnel. Authorized personnel include Manufacturing, Maintenance and certain Quality employees. The Senior Manufacturing or Quality Managers must admit all other individuals. All exit doors are locked from the inside, and access is controlled and documented through an electronic key card entry system. Personnel working in Process Development or Quality Control are not permitted in the Manufacturing facility on the same day they worked in the laboratories, unless they enter Manufacturing prior to working in those areas. Personnel cleanliness, gowning, and work activities are controlled. All personnel entering the facility must follow approved specified gowning requirements (SOP MG0007). Personnel must refrain from moving into work areas that are not being used for their specific assignment. Personnel may not move from baculovirus positive to baculovirus negative areas of the facility. Procedures for entry and egress of the facility are posted at the entrances to the facility.

Personnel are trained in gowning procedures and are required to follow instructions outlined in approved standard operating procedures prior to entering the manufacturing suites. Trained personnel are responsible for the movement of raw materials, media, buffer, and product throughout Building b(4).

All FluBlok drug substance manufacturing operations are performed in Building b(4)Meriden, CT. The manufacturing facility is located on the --b(4)-- and is approximately --b(4)------. The bulk manufacturing operations include: --b(4)-----

----- to a final monovalent bulk. The facility is designed to utilize USP (--b(4)-----) and DSP (--b(4)-----) batch processing steps to manufacture recombinant baculovirus derived protein products. In addition to bulk manufacturing (USP and DSP) the facility has dedicated buffer and media preparation suites, which are also located within the manufacturing suite of Building b(4) Manufacturing support functions such as equipment preparation, component washing and sterilization, and temperature controlled storage areas are also located on the --b(4)--- of the building, within the Manufacturing facility. The --b(4)----- of Building b(4) houses utility systems which service the Building b(4) manufacturing suite. Heating Ventilation and Air Conditioning (HVAC) units are located --b(4)--. The facility has a back up electrical generator to supply electricity in the event of a loss of utility supplied electricity.

To prevent mix-ups and cross contamination, appropriate control and changeover procedures are in place (see Section 3.2.A.1.1.7 below), and cGMPs are followed throughout the entire manufacturing process. All product contact equipment and accessories are cleaned appropriately or are single use. Only one product is allowed in a given area at a given time, and manufacturing areas are restricted to only those employees who require access. Additionally, the production areas have designated and isolated areas for specific unit operations. To help prevent product contamination, the facility is designed to promote essentially uni-directional product flow from the receiving and warehouse area through --b(4)--- -----

----- Air handling, water, environmental monitoring, and procedural systems are in place.

Utilities and Central Support Systems

This section provides information about the HVAC, steam systems, electrical generator, water systems, gases, and environmental monitoring. The utility systems in Building b(4) are qualified.

HVAC Systems

The manufacturing suites are divided into rooms designed for the work being performed and have the appropriate air rate exchanges to provide required levels of cleanliness. Classified rooms and manufacturing areas are maintained at class –b(4)--- with the exception of the Final Filtration room b(4) which is class –b(4)-- Class –b(4)-- hoods are used throughout the facility to perform aseptic manipulations.

The HVAC system is designed to have appropriate air exchange rates and cleanliness classification for the activities within the manufacturing suite. Air exchange rates –b(4)----- changes per hour are maintained for the areas qualified as Class –b(4)--. Baculovirus negative and baculovirus positive areas are segregated and controlled using air cascade, airlocks, and dedicated HVAC units to ensure that cross contamination does not occur. The baculovirus negative and baculovirus positive air handling units that service the production areas employ dedicated ducting which is not cross connected. In addition, re-circulated air never mixes between segregated baculovirus negative and baculovirus positive areas. Air is supplied to the controlled suites through terminal High Efficiency Particulate Air (HEPA) filters. The HEPA filters terminate at the ceilings with low wall air returns strategically located in each suite.

Air pressure differentials are maintained throughout the facility to ensure adequate environmental control. Rooms of higher cleanliness are designed to have a positive static pressure with respect to adjacent areas. To ensure containment, baculovirus positive areas are at a negative pressure relative to the adjacent air locks.

All of the manufacturing rooms are environmentally controlled as necessary to provide protection from contamination by dust or other foreign materials and to provide controlled conditions. Air pressure differentials are utilized to assist in preventing airborne contamination. Using constant pressure air-regulators, pressure differential is created when one room is maintained at a higher pressure than an adjacent room. The pressure differential monitoring equipment consists of sensors within the environmentally controlled areas and low point alarms to indicate when the pressure differential drops below minimum value.

Clean Steam System

The clean steam generator is dedicated to Building b(4) manufacturing operations, producing sufficient steam to meet service requirements. Clean Steam is generated from the USP quality feed water system and is used for –b(4)-- -----

----- . Clean steam is –b(4)-- -----

Water System

Water used in the manufacturing facility is USP quality and is utilized for housekeeping needs, glassware washing, buffers, media, and clean in place, and provides feed to the clean steam generator. In addition, it provides –b(4)– -----
----- The distribution loop is monitored to ensure that adequate water

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