



DATE: 10 November, 2008

FROM: Matthew Sandbulte
Maryna Eichelberger

THRU: Jerry Weir

CC: Anissa Cheung
Phil Krause

SUBJECT: BLA STN 125285/0

PRODUCT: Influenza recombinant HA trivalent

SPONSOR: Protein Sciences Corp

Summary:

Significant deficiencies were noted upon review of 3.2.S (Drug Substance) and 3.2.P (Drug Product). These include: insufficient characterization and incomplete validation of the drug substance manufacturing process; insufficient justification of the minimum potency specification; incorrect determination of release potency specification; additional information is needed for complete evaluation of some release tests. We recommend that the product not be approved and a CR letter issued so that deficiencies can be addressed.

Introduction:

This BLA is for licensure of baculovirus-expressed insect cell-derived recombinant hemagglutinin (rHA), under the trade name FluBlok. The biochemical name is “purified recombinant hemagglutinin (derived from H1, H3 and B strains)”. This trivalent product is a sterile solution with no added preservatives for intramuscular immunization. Each 0.5ml dose contains 135 ug (45 ug of each strain) rHA and will be for active immunization of adults 18 yrs and older. We have reviewed modules that describe manufacture and specification of drug substance (monovalent bulk rHA for H1, H3 and B strains) and drug product (trivalent formulation).

1. Manufacture sites and contract laboratories

Protein Sciences Corp., Meriden, CT: At this site, rHA monovalent bulk concentrates (drug substance) are manufactured; release tests of drug substance are performed; stability tests of drug substance are performed. PSC is also responsible for determining DNA content and lot release of drug product.

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

(b)(4)

A clinical lot consistency study (PSC04) demonstrated differences in immunogenicity of the H3 in spite of equivalent amounts of rHA added (based on SRID values). Investigation of the 3 different H3 monovalent batches showed that the 2 lots used to prepare lots that were less immunogenic had

(b)(4)

Process Validation Plan: The validation plan is included in the BLA as Attachments 1 (document P-VMP-2007) and 2 (addition to previous document describing conformance lot) in 3.2.S.2.5. The plan includes a general approach and states that all results of in-process tests and analytical results will be included in the validation report together with acceptance criteria. The masterplan does NOT include in-process tests to demonstrate product yield and quality at each step i.e. there are no test results to evaluate performance of each step. For example:

- (b)(4)

1 Page determined to be not releasable: b(4)

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

The HAI assay description is adequate. The assay that is described is 'standard': -----

1 Page determined to be not releasable: b(4)

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

6.2. Drug Product Specifications. Drug Product specifications are listed in 3.2.P.5 and shown in the Table 3.2.P.5.1 (included at the end of this report). Specifications for appearance, identity, endotoxin, and -----(b)(4)----- Specifications for drug product that are distinct -----(b)(4)-----:

Purity. (b)(4). While higher purity is the goal, (b)(4) is the lower limit of acceptable purity. Purity is calculated -----(b)(4)----- This calculation needs to be included in the formulation batch records or worksheet (included in CR letter comment #11b).

Baculovirus DNA: The specification listed for total or baculovirus DNA is inappropriate – it should be corrected to show a specification of ≤ 10 ng/trivalent dose. Figure 3.2.S.3-6 suggests the sensitivity of this assay is approx --(b)(4)--. This is appropriate for this assay. 3.2.S.3-6 shows results for baculovirus DNA content -----

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

----- We have requested total DNA content and information regarding --(b)(4)----- in CR letter comment #3g.

Total DNA: Assay description, validation and results have not been provided. This is requested and it is noted that the specification should be set at ≤ 10 ng/trivalent dose (not per strain, CR letter comment #10c).

Sterility testing is performed as per 21CFR 610.12. The proposed specification is “No growth observed,” as required by 21CFR 610.12. All batches used for clinical studies PSC01, PSC03, PSC04, and PSC06 have met this specification.

Potency specification is stated as -----(b)(4)----- for each HA component (H1, H3, and B)”. The minimum potency specification of ----(b)(4)--- that is proposed is unacceptable as it has not been justified nor demonstrated by clinical data. We have asked the firm to support the minimum end-expiry potency specification with clinical data (CR letter comment #3a).

FluBlok has shown significant immunogenicity across these previous studies, and the study results indicate that recombinant rHA vaccines may be significantly more immunogenic than the standard egg-grown inactivated vaccine when used at higher antigen concentrations. PSC has released drug product for clinical studies PSC03, PSC04, and PSC06 with a potency specification of 45 μ g ---(b)(4)--- as measured by SRID per dose. All formulation, release, stability and validation work to date has been performed using this specification. At the request of the FDA at the September 21, 2007, preBLA meeting, however, PSC tightened the specification for release of drug product to -----(b)(4)----- for each HA component (H1, H3, and B)”. It would be more accurate however to list the specification as the targeted dose of 45 μ g/dose, with the understanding that assay variability may result in commercial drug product at (b)(4) of this value. The sponsor needs to have a target dose (45 μ g/dose) and then formulate to meet that target dose at expiry (i.e. take into consideration stability). This comment is included in CR letter #3b. The SRID doses used in clinical trials (Table 3.2.P.5.6-2, included at the end of this report) shows the potency values for drug product batches released

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

Table 3.2.S.2.6-4 Drug Substance Batches Used to Formulate Trivalent Drug Product Batches in FluBlok Development

Year of Manufacture (Study Number)	Drug Product Composition and Batch Number	Drug Substance Batches by Subtype and Strain		
		H1	H3	B
2003 (DMID 03-119)	Composition	A/New Caledonia/20/99	A/Panama/2007/99	B/Hong Kong/330/2001
	0316P-A	(b)(4)	(b)(4)	(b)(4)
	0316P-B	(b)(4)	(b)(4)	(b)(4)
	0316P	(b)(4)	(b)(4)	(b)(4)
2004 (PSC01)	Composition	A/New Caledonia/20/99	A/Wyoming/3/03	B/Jiangsu/10/03
	50-04011A	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	50-04011B	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
2006 (PSC02 & PSC03)	Composition	A/New Caledonia/20/99	A/Wisconsin/67/2005	B/Ohio/01/2005
	50-06019 (PSC03)	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	50-06020 (PSC02)	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
2007 (PSC04 & PSC06)	Composition	A/Solomon Islands/03/2006	A/Wisconsin/67/2005	B/Malaysia/2506/2005
	50-07010 (Lot A)	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	50-07011 (Lot B)	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
	50-07014 (Lot C)	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----

1 Page determined to be not releasable: b(4)

Table 3.2.P.5.1-1 FluBlok Drug Product Specifications

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)----
Sterility	Membrane Filtration (21 CFR 610.12)	No growth observed
Potency	SRID (PR-1468)	----(b)(4)--- -----
Purity	Weighted Average of Drug Substance Purities	----(b)(4)----
DNA Content	----(b)(4)--- -----	----(b)(4)----
	----(b)(4)--- -----	
----(b)(4)----	----(b)(4)----	----(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 labeled volume

Table 3.2.P.5.6-2. Potency Data on Batches of Drug Product at Release. Potency was measured by SRID. Target formulation was 45µg/dose and actual result per batch is shown below. Potency (as measured by SRID) specification was 45µg/dose --(b)(4)--- for PSC03, PSC04, and PSC06 batches.

Purpose	Year of Manufacture	Batch Number	H3 Potency (µg/dose)	B Potency (µg/dose)	H1 Potency (µg/dose)
PSC01 Trial	2004	50-04011A	45	45	36 ¹
PSC03 Trial	2006	50-06019	48	42	44
PSC04 & PSC06 Trial	2007	50-07010 (Lot A)	44	50	41
	2007	50-07011 (Lot B)	50	48	46
	2007	50-07014 (Lot C)	42	44	44
Process Validation/Stability	2007	CM7-515	44	48	45

¹ After formulation of Batch 50-0411A, it was determined that the concentration of the H1 component in the high-dose formulation was 35 µg, rather than the target dose of 45 µg. This deviation was reported on October 12, 2004 (Memorandum from Manon Cox, COO to Director DVRPA) in an amendment to BB-IND 11951 (Serial 2 dated 10/12/04).