

Mid-Cycle Review Meeting Summary

BLA: STN 125285/0
Manufacturer: Protein Sciences Corporation
Proper Name: Influenza Vaccine
Proprietary Name: FluBlok®
Meeting Date: July 13, 2009 12N – 1 pm

Submission Format: Paper and electronic

Milestones:

Received:	18-Apr-2008
Complete Response:	29-Aug-2008
Resubmission:	28-Apr-2009
Action Due:	28-Oct-2009

Attending BLA Review Team:

Rakesh Pandey	Chair
Katherine Matrakas	Regulatory Project Manager
Timothy Fritz	Regulatory Project Manager
Maryna Eichelberger	Product
Rajesh Gupta	Other
Arifa Khan	Product/Cell Substrate
Barbara Krasnicka	Biostatistics
Cynthia Nolletti	Clinical
Patricia Rohan	Epidemiology
Matthew Sandbulte	Product
Deborah Trout	CMC, Facilities

Non-attending BLA Review Team Members:

Marion Gruber	Developmental Toxicology
Jean Makie	Advertising and Promotional Labeling
Lev Sirota	Assay Validation Statistics
Robert Wesley	Bioresearch Monitoring

Other Attendees:

Norman Baylor
Jerry Weir
Andrea Sutherland
Lewis Schragger

Meeting Summary-

The discussion focused on outstanding CMC, clinical and statistical issues. It was decided that the CMC information request (IR) should be conveyed to PSC as soon as possible. While it was mentioned that presentation of FluBlok at the September 11, 2009

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VRBPAC might not be warranted, a final decision was not made. It was also noted that, due to the extensive nature of the CMC IR, the sponsor's response may be classified as a major amendment and 3 months would be added to the review clock (due ~ Jan 2010).

Resubmission Review Cycle Timetable:

Event	Date
VRBPAC Planning Meeting	June 9
VRBPAC Discussion Meeting	June 30
Internal PREA Decision	July 12
Mid-Cycle Review Meeting	July 13
Draft Review Memos Due	July 27
Proprietary Name Review	?
PeRC Presentation	August 12
First Labeling Meeting	?
VRBPAC Briefing Documents Due to CBER Management	July 24
Final Reviews Due	August 26
Determination of PMCs/PMRs	?
Notify FDAAA SWG of PMRs	?
RPM begin draft of Action Letter	September 23
1 st VRBPAC Run-Through	August 26
Action Package to Management	September 30
2 nd VRBPAC Run-Through	August 31
VRBPAC	September 11
Action Due	October 28
Action Package to OCOD for Web Posting	October 28

2009 Resubmission CBER Correspondence with PSC:

CMC IR (H3 validation)	May 27
Statistical IR (SAS programs)	June 9
VRBPAC items	June 16
Clinical IR	June 19

2009 Resubmission Amendments Submitted to the BLA:

12	Partial response to CR letter
13	Resubmission
14	483 response to pre-licensing inspection
15	SAS programs (Response to June 9 IR)
16	Interim H3 validation (Response to May 27 IR)
17	Response to June 19 Clinical IR

Mid-Cycle Review Status Updates:

General Discussion-

Norman Baylor- Asked whether the reviews were sufficiently complete to make a determination of whether a CR or IR letter should be issued. Rakesh Pandey indicated that discussion within DVRPA had generated some agreement that the list of issues for IR is too extensive to be adequately addressed in time for 11 September VRBPAC.

Jerry Weir- Felt that although the CMC IR requests were numerous, the sponsor would be able to address them in a timely manner (2 - 3 months *versus* 6 months - 1 year) but wanted to hear concerns from individual reviewers expressed during the meeting.

Maryna Eichelberger - Product CMC

I have read through their responses to each of the CR letter CMC comments and the 2009 process validation report that was submitted mid-June. I focused on identifying deficiencies in their response to process validation and process characterization. The list of questions that the sponsor needs to answer for complete review of the submission was submitted to DVRPA 19th June 2009. The major CMC issues that I am aware of are:

- Insufficient data submitted to support process validation
- Column re-use: no data provided to support use of the same column for different HA strain preparations; and product yield not considered in re-use studies.
- Poor product stability means that:
 - Potency is a ‘moving’ target, with a dose of ---(b)(4)---- per HA strain acceptable at expiry
 - Product is -----(b)(4)----- per strain, with upper specification of (b)(4). Safety data from DMID 03-119 used to support the safety of this dose even though the product manufacturing process and purity is significantly different.
 - Shelf-life is 16 weeks; monovalent bulk is also not very stable but specifications are set loosely resulting in product formulated early after manufacture with significantly less protein (and consequently less impurities) than product formulated later in the season.
 - **Discussion- While most CMC issues included in the IR letter could be answered relatively quickly, the questions concerning aggregate formation may take a fairly long time to answer. Concern was also expressed regarding the short shelf life of FluBlok and the possibility of requesting a commitment (PMC) for stability data was raised.**

Matthew Sandbulte - Product CMC

In PSC's responses to Comment 3 they describe a revised approach to setting and meeting rHA potency specifications. Potency of FluBlok delivered to volunteers in the supporting clinical trials has been re-estimated using linear regression to account for decay between formulation and the median day of vaccination. Using these estimates, a

minimum potency of ----(b)(4)----- through expiry has been proposed. PSC anticipates meeting this lower limit by formulating to ----(b)(4)----- . However, there appear to be significant flaws in the calculations, and we have submitted questions (19 June 2009) aimed at addressing them before we can accept the 16 week expiry. We also seek clarification on release specifications for SRID potency and total protein in----- (b)(4)----- and FluBlok product. There are also concerns about assays for DNA quantification and -----(b)(4)----- in drug product, which we have pointed out in the same set of questions.

Discussion- Some concern was expressed regarding the robustness of the assays used for DNA quantitation -----(b)(4)-----.

Arifa Khan –

I have reviewed PSC’s responses to Comment 5 regarding information that was requested in the CR letter to complete the review of the Adventitious Agents testing of the cell substrate and the product. I provided a written request for additional information to complete the review of the submission in a memo sent to DVRPA on June 18th 2009. The major points to be addressed were related to the results of the ----(b)(4)----- assays.

- Sensitivity and validation report of the –(b)(4)- assay used to evaluate the MCB and EOP cells
 - -----

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

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- -----(b)(4)-----
 - -----
-----**(b)(4)**-----
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Deborah Trout - Facility CMC, Inspector

- 483 - a few outstanding issues that still need to be resolved
 - **Discussion- It was felt that scheduling of a second inspection should wait until the sponsor had received and had an opportunity to respond to IR letter issues. Scheduling of the follow-up inspection would take approximate 2 weeks with the actual inspection taking 2 – 3 days. The EIR could be completed the following week.**
- EIR not complete
- Review memo done
- CR response review memo done (outstanding issues to be communicated in IR letter)
- Environmental Assessment memo - not done
- Inspection Waiver for Hospira - not done

Cynthia Nolletti - Clinical

- Failure of B strain to meet immune response and non-inferiority endpoints in older adults
- Protective efficacy demonstrated only in the pivotal trial against placebo and against antigenically mismatched strains (H3N2 > B). Another small trial suggested protective efficacy against placebo. Is this sufficient data on which to grant traditional approval?
- Traditional versus accelerated approval?
- Need for additional clinical endpoint data as PMC?
 - **Discussion- The submission by PSC of efficacy data (Study PSC04) may warrant a change from accelerated approval to traditional approval. Due to strain mismatch, CBER may request another PMC efficacy study, perhaps in the elderly or pediatric populations.**
- Pediatric study very small, no source data, synopsis suggests poor immunogenicity especially in 6-34 mos. Deferral and waiver requested, Pediatric Plan not very detailed. IR request June 19, 2009 for more details to satisfy PeRC. PSC plans to submit detailed plan by July 30, 2009.
- Failure of lot-to-lot consistency for the H3 antigen.
- Applicant response to Clinical Comments in the CR letter appear satisfactory overall, but await Statistical Reviewer opinion on some issues:
 - PSC03 and PSC06 may not have had adequate power to demonstrate non-inferiority endpoints
 - Variability of GMTs between and within lots
 - PSC04 designed to evaluate primary efficacy endpoints and test formal null hypothesis against antigenically matched strains. Do the VE conclusions regarding performance against mismatched strains have sufficient statistical power?
- Review of the data submitted to the BLA has not revealed significant safety concerns.

Barbara Krasnicka - Biostatistics

- **Discussion- A list of IR comments will be provided regarding lot-to-lot variability and interim and final subject distribution.**

Patricia Rohan - Epidemiology and Pharmacovigilance

- **Discussion- Noted that PSC planned to submit a pharmacovigilance plan 1 year after approval which would enroll 100,000 subjects from which data would begin arriving after 2-3 years.**

Lev Sirota - Clinical Assay Statistics (No update, did not attend, on leave)

Rajesh Gupta- Product Testing

Discussion- Lot release protocol- H3 lots issues with stability; on hold now for testing in support, testing plan and lot release protocol. Rajesh indicated that once manufacturing issues are resolved and the formulation target is finalized, 3-5 lots of monovalent bulks and 3 lots of final formulated bulks manufactured using validated and final process need to be submitted to CBER for testing.

Rajesh indicated that the testing plan could be finalized once testing in support was completed and also indicated that the lot release protocol could also be finalized once CBER had received and tested samples of monovalent bulks and final formulated bulk for in-support testing.

Robert Wesley - Bioresearch Monitoring

- There were no BIMO issues during the initial phase of this BLA; a Summary memo to that fact was submitted in Aug of 08. Nothing has changed, there are still no BIMO issues.

Marion Gruber – Pharmacology, Developmental Toxicology

- I have read the sponsor's response regarding pharm/tox questions 25, 26, 28 and 28 in the CR letter (developmental tox study 2146-001). There are no additional issues to be discussed with sponsor.

Jean Makie - Advertising and Promotional Labeling (No update, did not attend, on leave)

Katherine Matrakas - Regulatory Project Manager

Timothy Fritz - Regulatory Project Manager

PeRC

Scheduled for August 12, 2009

VRBPAC

Planning Meeting held June 9. Duties and tasks assigned and are being coordinated by Katherine Matrakas, Christine Walsh and Marion Gruber. We are on schedule and relevant experts have been identified. Drs. have been invited to serve on FluBlok VRBPAC. Chris Walsh is working with them for necessary conflict of interest screening. A decision was made not to invite an insect cell line expert. Other activities are proceeding on schedule. Norman indicated that this file may not be ready to go to VRBPAC due to product and clinical/statistical issues and that he would speak with Wellington to finalize the decision in order to inform the sponsor in the future (after IR comments sent to sponsor).

Discussion- In relation to the BLA's likelihood of being ready for VRBPAC, Matthew Sandbulte reiterated that the Sponsor's antigen filling requirements and dating period calculations seem in need of revision. Dr. Baylor inquired whether revised calculations may fail to support the 16 week expiry. MS affirmed that this is a possibility.

Review Memos

Please note the following request for important information regarding your Review Memo(s):

- On the first page, please list:
 - the sections of the BLA reviewed

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- each Amendment number reviewed
- any Information Requests you asked for from PSC
- which Amendment responded to your request, and
- whether the response was acceptable