

Midcycle Meetings Minutes Final, October 16, 2012 - Flublok

DEPARTMENT OF HEALTH & HUMAN SERVICES
Service

Public Health

Food and
Drug Administration

1401 Rockville Pike

Rockville, MD 20852-1448

RESUBMISSION MID-CYCLE MEETING SUMMARY

Date and Time: October 16, 2012, 2:30 pm

Location: WOC2-3101/3103

Call-In Information: —b(4)-----

STN: 125285/0

Submission Type: Original Application, Complete Response

Sponsor: Protein Sciences Corporation (PSC)

Product: Flublok® [Influenza Vaccine]

1. ATTENDEES

Review Team

Name	Review Role
Timothy Fritz, Ph.D.	Chairperson
Helen Gemignani	Regulatory Project Manager
Kristina Carroll, Ph.D.	Regulatory Project Manager
Cynthia Nolletti, M.D.	Clinical
Maryna Eichelberger, Ph.D.	CMC, Product
Arifa Khan, Ph.D.	CMC, Product
Barbara Krasnicka, Ph.D.	Biostatistics, Clinical
Lev Sirota, Ph.D.	Biostatistics, Clinical Assays
Karen Campbell	Quality Control, CMC/Lot Release
Rajesh Gupta, Ph.D.	Quality Control, CMC/Testing
Deborah Trout Assessment/Categorical Exclusion	CMC/Facility, Environmental
Jane Woo, M.D.	Epidemiology, Pharmacovigilance

Others

Marion Gruber, Ph.D. Reviewer	Director, OVRP; Reproductive Toxicology
Wellington Sun	Director, DVRPA
William McCormick	Director, DBSQC
Anissa Cheung	OVRP/DVP

Tsai-Lien Lin	OBE/DB
Theresa Finn	OVR/IOD
Rakesh Pandey	OVR/DVPA
Amelia Horne	OBE/DB
Robin Levis	OVR/DVP

2. BACKGROUND

On July 17, 2012, PSC submitted a complete response to CBER's January 11, 2010, Complete Response Letter. Flublok is a recombinant hemagglutinin influenza vaccine indicated for active immunization of adults 18-49 years of age against seasonal influenza disease caused by influenza virus subtypes A and type B represented in the vaccine.

3. IMPORTANT DATES

Resubmission Received:	July 17, 2012
Filing Action:	September 15, 2012
Midcycle Meeting:	October 16, 2012
PeRC Presentation:	October 24, 2012
Final Reviews Due:	November 29, 2012
PMC Study Target:	November 24, 2012
Labeling Comments to Sponsor:	December 9, 2012
Action Due Date:	January 16, 2013

- VRBPAC Meeting held on November 19, 2009

4. MEETING AGENDA

4.1 Mid-cycle Review Status Updates by Discipline

CMC Product, Facility, and Testing

- **Arifa Khan (CMC Product)**

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- Further internal discussions are needed to discuss the significance of these findings.

- **Maryna Eichelberger (CMC Product)**

- A recent amendment was submitted containing additional stability data to support a longer shelf life for Flublok. The data is under review.

- **Deborah Trout (CMC Facility)**

- Another inspection of PSC's Meriden, CT facility is scheduled for Nov 5.
- OCBQ will perform the compliance check for PSC.

- **Karen Campbell, Rajesh Gupta (QC, Lot Release, Testing)**

- Lot release protocol recommendations have been sent to the sponsor.
- In-support testing has been completed.
- Additional monovalent samples and launch lots are expected soon.

Clinical Studies and Biostatistics

- **Cynthia Nolletti (Clinical)**

- Draft review of the original submission and first CR were completed January 2010. Minimal changes have been made to text and major changes made to most tables to make 508 compliant. An Addendum to the review has been written summarizing updated information and issues that have been addressed since the January 2010 CR letter. Updated drafts are with RPMs and Branch Chief.
- Key clinical issues have already been discussed internally and with the sponsor: limiting the age indication to 18-49 years of age in this review cycle and postmarketing studies to support licensure in persons 50 years of age and older.
- Postmarketing studies under consideration:
 - Phase 3 study(ies) to extend the indication to persons 50 years and older.
 - Phase 4 observational safety study in persons 18 years and older (2 PMCs will be tracked: 18-49 and ≥50 years) – discussion and details deferred to Dr. Woo. Sponsor originally submitted the study concept as part of the pharmacovigilance plan in the original submission, April 2008. There was discussion about whether this study is a PMR or a PMC. Although there is no clear safety signal in the database, the database is small and may not be sufficient to detect a signal. The one case of pleuropericarditis does not seem to be related, but we cannot exclude with certainty the possibility that it was an idiosyncratic reaction or an immune-mediated adverse reaction related to Flublok. The small safety database does not reveal an imbalance of hypersensitivity events, but this is a novel vaccine produced in insect cell culture and the potential for hypersensitivity reactions particularly with repeat exposure should be evaluated in a larger population post-licensure. OVRP will discuss with OBE the need to request that manufacturers commit to conduct post-marketing safety studies in the absence of a known risk, signal or potential signal as described in FDAAA 2007.
- Additional data to support the HAI validation and comparability of BEVS and egg-derived antigens.
- PREA studies – two pediatric PMRs.
- Proposal for pregnancy registry – details and discussion deferred to Dr. Woo.
- We are awaiting a decision from PSC regarding single VE/safety study or separate RCTs of safety and VE in persons 50 years and older. Submission of a protocol for the safety study that the sponsor wants to start in January is expected.
- Response to IR is awaited: Sub-analyses with CIs for gender, race and ethnicity.
- Updated Pediatric Plan will be presented to the PeRC on October 24, 2012.
- Awaiting 2 PREA protocols (PSC08 and PSC12) – synopses have been submitted; it is acceptable for PSC to submit formal protocols and SAPs after the PDUFA due date.
- PSC has indicated in the pediatric plan that a pediatric clinical endpoint study has been requested by the EMA. We may receive more information regarding this study just prior to the PeRC meeting next week.
- The first labeling meeting was held on October 16, 2012. We should be able to complete the internal labeling revisions at the next meeting on October 24, 2012 and then send the revised draft to PSC.

- **Barbara Krasnicka (Clinical statistics)**

- The first statistical review based on the original submission, and the responses to the IR and CR letters (submitted 08/09) were completed in December 2009.
- The statistical review is being revised:
- Tables have been changed to be 508 compliant.
- Issues discussed lately have been incorporated in the statistical assessments of results.

Clinical Assays

- **Lev Sirota (Biostatistics)**

- No bioassay information was provided in PSC's complete response so there were no new updates.

Pharmacovigilance

- **Jane Woo (Epidemiology)**

- Pregnancy Registry comments are being drafted.
- Whether CBER will request PSC to conduct their large, Phase 4 general safety study as a PMC will be discussed at the Center level before a decision is made.

5. SIGNIFICANT ITEMS OF NOTE

- If approved this cycle, Flublok use will be limited to persons 18 to 49 years of age.
- Additional internal discussion is needed regarding the significance of the b(4) data.