

Record of Telephone Conversation, June 12, 2008 - Flublok

- Submission Type: BLA
Submission ID: 125285/0
Office: OVRP
Product: Influenza Vaccine
Applicant: Protein Sciences Corporation
Telecon Date/Time: 12-Jun-2008 04:15 PM
Initiated by FDA? Yes
Communication Category(ies): 1. Information Request
Author: RAKESH PANDEY
Telecon Summary: Statistical and clinical comments RE:PSC04; Clinical comments RE:PSC06; CMC comment.
FDA Participants: Rakesh Pandey
Non-FDA Participants: Manon Cox
Telecon Body:
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Draft Information Request Comments on BLA 125285

Statistical Comments Regarding Study PSC04:

1. Please explain how subjects were selected into the serology subset at six sites.
2. According to the last version of the PSC04 protocol, you planned to enroll at least 150 subjects per lot (all together 450 subjects in the immunogenicity subset) to establish lot-to-lot consistency. However, only 393 subjects have Day 28 HI titers. Per your data set "sero.xpt," 50 more subjects had baseline HI titers. Please explain why there are no data for Day 28 HI titers for these 50 subjects (11% = 50/443) from the immunogenicity subset.
3. The HI antibody responses for three strains contained in the vaccine were assessed by b(4) HI assays. Please explain why so many HI assays were used and how serum was assigned to each assay.
4. Based on your Table 6 (page 56 of 419), Protocol Deviations through the Day 28 Visit/Phone Call, it seems that 50 subjects with baseline HI titers but without Day 28 HI titers and 2 subjects with Day 28 HI titers but without baseline HI titers were not included in this table. Please comment.
5. In connection with Table 11 (page 66 of 419), please define clearly what you mean by "pre-vaccination titer below limit of detection at the baseline" and "Seroconversion or Significant Increase in HAI Titers at the Day 28 Visit."
6. Please show that adjusting for lots does not have influence on the CIs of seroconversion rates. Additionally, please submit a SAS program that you will use for this analysis.
7. The title of your Table 14.2.2.5 is "Determination of Lot Consistency at Day 0". However, this table shows only baseline GMTs per lot. Please comment.

Clinical Comment Regarding Study PSC04:

8. Please submit in tabular form a summary of all Unsolicited AEs from Day 0 through Day 28 according to Lot assignment. Please categorize AEs according to MedDRA System Organ Class and Preferred Term and according to severity grade. Please submit these data by close of business June 26, 2008 or at your earliest convenience.

Clinical Comment Regarding Study PSC06:

9. Fever as a reactogenicity event is described in Module 5, Volume 26, text p.61 and Table 14 p.62. You report only one case of fever ≥ 100.4 reported among all 602 subjects. This occurred in a FluBlok recipient and was of mild severity. CBER has evaluated the datasets (PSC submission 125285.0/3, 5/19/08, file named DT, Reactogenicity Memory Aid) for the occurrence of fever and found that 593 subjects recorded their temperature in the diary card on 4705 occasions between Day 0 and Day 7. Of these, all 4705 temperature recordings appeared to be associated with the symptom of fatigue or lack of energy. No temperature appeared to be recorded concomitantly with other symptoms such as shivering or chills. Of the 4705 recorded temperatures, only four were above 100.4° and are presented in the table below:

**Table Fever $\geq 100.4^{\circ}\text{F}$ Day 0 to Day 7 – Electronic Datasets
PSC06 Safety Population**

Patient ID	Group	Day	Temperature $^{\circ}\text{F}$
0258	FluBlok	2	100.4
0275	FluBlok	1	100.6
0656	TIV	3	100.4
2058	FluBlok	4	100.4

Please explain the discrepancy between the applicant's report and the reviewer's findings of the number of subject with fever $\geq 100.4^{\circ}\text{F}$. Please also explain why the datasets suggest that temperature was recorded only in association with subjects who reported fatigue, lack of energy. Please submit these data by close of business June 26, 2008 or at your earliest convenience.

Additional Comment (CMC):

10. Please provide all product and clinical data for vaccine lots that have been used in clinical trials in a tabular form. This table should list: clinical study number with age range and # of vaccinees; the lot numbers of each trivalent formulation; the potency of each antigen and the method of assay; the lot numbers for each monovalent bulk component in each vaccine preparation; the amount of antigen in each lot measured by SRID; the amount of antigen in each lot measured by ----- (b)(4)-----; the total protein concentration in each lot; the purity of the preparation (percent HA and also percent host cell protein); the GMT for each antigen in the vaccine before and after vaccination with each lot; the percent responders (4-fold rise) to each antigen and the percent of individuals with titer ≥ 40 before and after vaccination.