# Summary of Bioresearch Monitoring Inspections – AFLURIA

**MEMORANDUM**
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
DATE
September 5, 2007
FROM
Bhanu Kannan, Bioresearch Monitoring Branch, HFM-664
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
THROUGH
Patricia Holobaugh, Chief, Bioresearch Monitoring Branch, HFM-664
TO
Rakesh Pandey., HFM-478
Chair, BLA Licensing Committee
SUBJECT
**Summary of Bioresearch Monitoring Inspections**
SPONSOR: CSL Limited
PRODUCT: CSL Influenza Vaccine-with or without thimerosal
BLA: STN 125254/0

**Summary**

The bioresearch monitoring inspections of three clinical investigators did not reveal significant problems that impact the data submitted in the Biologics Licensing Application (BLA). The problems found during the inspections are noted in this memorandum. Two of the clinical sites had deficiencies in documenting the storage temperatures of the study vaccines.

**Background**

Inspections of three clinical sites were requested in support of the BLA and were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspection assignment included specific questions on the following study protocol entitled *A Phase III, Randomized, Double Blind, Placebo-Controlled, Mutilcenter Study to Evaluate the Immunogenicity, Safety, and Tolerability of CSL Limited inactivated Influenza Vaccine in Adults ≥ 18 to < 65 Years-Protocol CSLCT-FLU-05-09 (DMID 06/0016)*.

The inspections were conducted at three clinical sites and represented 28% of the total subjects enrolled in the study for which the sponsor has submitted data in the BLA. The data audit portion of the inspection focused on the verification of the study data on safety, efficacy, and the immunogenicity endpoints submitted by the sponsor in the BLA for a randomly and equitably selected subjects from the total number of enrollees at the site. The following table identifies the inspection results.

**Inspection of clinical sites and outcome**

| Clinical investigator | Study site / Site # | Location | Number of subjects enrolled | Form FDA 483 issued | Final classification |
|---|---|---|---|---|---|
| Kathryn Edwards M.D. | Vanderbilt University /14 | Nashville, TN | 160 | Yes | VAI |
| Emmanuel [Chip] Walter, M.D | Duke University /15 | Durham, NC | 90 | No | NAI |
| Cornelia Dekker, M.D. | Stanford University /16 | Stanford, CA | 133 | Yes | VAI |

VAI - Voluntary Action Indicated
NAI - No Action Indicated

We received the inspection report for sites #14 and 15 (Drs. Edwards and Walter). The inspection report for Dr. Dekker (site #16) is pending. The following summary is based on a review of the inspection reports for the inspection of Drs. Edwards and Walter, and the emails and discussions with the FDA investigator for the inspection of Dr. Dekker.

***Inspectional findings***

**Clinical investigator (CI) issues:**

1. Failure to ensure that an investigation is conducted according to the investigational plan. [21 CFR § 312.60].
   A. Section 6.4 of the Manual of Procedures in the investigational plan required that study vaccines be stored under temperature monitored conditions of 35.6°F to 46.4°F (2°C to 8°C) in a secure area and that vaccines must not be frozen. Two clinical investigators failed to follow the protocol for the storage of the study vaccines and did not maintain adequate records for the storage of the vaccines and/or stored them under improper storage conditions, namely, storing them in the freezer instead of a temperature monitored refrigerator. [21 CFR § 312.60]

   ***Dr. Edwards:*** Temperature monitoring records were not maintained for the clinic refrigerator where the study vaccines administered to 101 subjects were stored from the start date of 6/12/06 through 6/28/06. During the inspection it was noted that while the vaccine administrator maintained such a log on the clinic refrigerator it was not being filled out and hence there were no documentation. The sponsor's monitor noted this problem and the sponsor subsequently added an additional 101 subjects at this site.

   ***Dr. Dekker:*** Our inspection noted that Dr. Dekker's site did not maintain adequate records for the storage of vaccines at the clinic as required by the protocol for all study subjects that was not reported by the sponsor in the BLA. In a note to file at Dr. Dekker's site the pharmacy indicated that the temperature in the cooler where the vaccines were stored stayed between 2°C and 6°C degrees. However, no temperatures were recorded for the storage of the vaccines at the clinic.

   B. Section 6.5 of the Manual of Procedures in the investigational plan required that separate Test Article Accountability Records be maintained for

each lot of the 5 study products and further described in detail the how the accountability records will be maintained for the multiple dose vials and the pre-filled syringes. Dr. Edwards did not maintain adequate test article accountability records as required by the investigational plan. A note to file completed by the unblinded vaccine administrator at Dr. Edwards' site said the site did not maintain such accountability records until pointed out by the monitor during a monitoring visit on 6/29/06. The site corrected the procedures and started maintaining adequate drug accountability records starting 7/6/06.

C. Our inspections verified the minor protocol deviations such as use of an influenza vaccine within six months (Dr. Dekker), use of prohibited medication such as Prednisone during the study (Drs. Edwards and Walter), out of acceptable window study visits (Drs. Edwards, Walter, and Dekker), blood draw on incorrect visit and/or insufficient blood draw (Drs. Dekker and Edwards), and non-availability of adverse event (AE) memory aid on study visit days (Dr. Dekker). These protocol deviations were reported by the sponsor in the BLA Listings 16 and 17.

D. Section 2.4 of the Manual of Procedures included in the investigational plan described regulatory requirements to be followed by the investigators in conducting research. For example, the procedures required that a copy of the current IRB approved consent form will be used to obtain informed consent from the subject. As noted by the sponsor in the BLA and verified by our inspection for at least 17 subjects the investigator (Dr. Edwards) did not use the IRB date stamped informed consent in obtaining the consent. The text of the consent form was the same but lacked the approval stamp.

2. Notable issue: At Dr. Walter's site at least four subjects (subject #s 004, 034, 049, and 064) were family members of the study personnel including two subjects that were family members of each of the unblinded study personnel. Further, in one of the instances, the vaccine was administered by the unblinded vaccine administrator to her own family member.

**Sponsor issues:**

3. The sponsor described a detailed monitoring plan dated 6//6/06 that was submitted in the BLA. We note that this plan was submitted by the sponsor in response to our (BIMO) request during the pre-BLA meeting. However, the sponsor did not ensure that the monitoring plan was adequately followed by the ---------- monitors as there were inconsistencies in site monitoring as described below. The vaccine storage deviations for 101 subjects were noted during a monitoring visit on 6/29/06 by a ---------- monitor at Dr. Edwards' site. However, at Dr. Dekker's site, the nine blinded and five unblinded monitoring visits by the----------monitor failed to identify that the site did not document the vaccine storage temperature prior to administration. Our inspection revealed that the pharmacy records indicated the date and not the time the vaccines were dispensed to the clinic. No temperature records were maintained by the clinic and the pharmacy for the storage of vaccines at Dr. Dekker's site.

4. **Electronic systems used in the study and data management:**

A. The sponsor described their data management practices in section 3 of the Manual of Procedures. The ----------

----------participated as the Data Coordinating Center (DCC) for the study and managed numerous data entries through the ---------- We note that the sites documented relevant observations in hard copy source documents and transcribed them to hard copy case report forms (CRF) and electronic CRFs (eCRF) as described in the sponsor's procedures. Further, a footnote in the CRF indicated that some observations such as the subject's health status in the Visit Documentation form were not captured on the -------. In some cases DCC requested data entry corrections from study sites and in other cases the monitor requested such corrections as shown in the examples below. We cannot determine who was authorized by the sponsor to make such requests.

i. At Dr. Dekker's site (#16) at least in four cases the monitor (----------) requested the clinical investigator to change the source document after the database lock for the study on 10/24/06. During the discussions with Dr. Dekker our inspection noted that study data were initially recorded on paper case report forms (CRF) entries and that they were entered into electronic CRFs (eCRFs) through an internet based software system within the sponsor specified time frame of 72 hrs after a subject's respective study visit. We do not know whether Dr. Dekker verified the eCRF entries when they were entered. After the data lock the following changes were made to the site source documents at Dr. Dekker's site, but these data were not changed in the clinical database because it had already been locked for analysis These are examples relayed by the FDA investigator who did the inspection, but we have not verified these because the inspection report has not been received by our office:

- For subject #040 for visit 3 the data entry for the new concomitant medications was changed on 4/5/07 from "Yes" to "No" although the eCRF indicated the subject as taking new concomitant medication, Seroquel.
- For subject #040, a comment in the medical history was changed at the request of the monitor on 4/4/07 to indicate that the subject did not have any influenza vaccination in the past 5 years. However, the eCRF indicated "Doesn't know" for the question of past influenza vaccination.
- For subject #064, the site changed the induration measurement on the reactogenicity record to "1" from "0" as recorded on the eCRF for day-3 on 1/26/06.
- For subject #116, the monitor requested the site to change the temperature for day-3 to 97.0°F for 97.1°F.

ii. At Dr. Edwards' site, the inspection revealed that the listing of adverse events that indicated multiple single symptoms were sometimes changed to a single diagnosis encompassing all of the individual events, based on a request from the sponsor,as illustrated in the following example: (a) For subject 031 the symptoms fever, diarrhea, body ache, and chills with onset dates differing by a day were changed to the diagnosis of "viral infection" nearly a month later at the request of the study monitor; and (b)

For subject 035, the symptoms nausea, vomiting, and diarrhea with the same onset date were changed to "viral gastroenteritis" two weeks later at the request of the monitor.

iii. Study records at Dr. Walter's site also note changes as note to file dated 12/20/06 after the database lock. At least one change was added to the source document on 3/28/07 after the data base lock that includes an adverse event.

We note that the data changes requested by the monitor after the data lock did not appear to have any impact on the outcome of the study data. However, it is not clear why the monitor/DCC would request such changes at the site after the data base lock and data submission to FDA. We recommend that the sponsor be advised that such requests and changes could compromise the data integrity.

B. Our inspection at Dr. Dekker's site noted that the site did not have access to the audit trail for any changes made by the study personnel. It appears that ---------- and the sponsor may have audit trails for any changes made to the web based electronic system entries. The investigational plan under section 16.1.1 stated that clinical data will be entered into a 21 CFR Part 11-compliant ------ provided by ----------. The computer system used during this trial was not thoroughly investigated as part of these inspections.

C. An email communication from ---------- dated 8/9/07 sent during the inspection at Dr. Dekker's site indicated that their (----------) data base had some audit trail errors due to various time zones not synchronized. ---------- informed all the study personnel at multiple institutions on 8/9/07 subsequent to the identification of the issue during the FDA inspection at Dr. Dekker's site that they are performing a patch to the software and that the issue will be resolved after the re-release of the software.

We recommend that for all ongoing and future clinical trials sponsored by DMID that uses computerized systems in clinical trials the sponsor(s) refer to the Guidance document, http://www.fda.gov/cder/guidance/7359fnl.pdf, for additional information on computerized systems used in clinical trials.

**BIMO actions**

We will issue letters to Drs. Edwards, Walter, and Dekker. Should you have any questions or comments about this memo or any aspect of Bioresearch Monitoring, please contact me at 301-827-6188.

/Bhanu Kannan/
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