M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: March 20, 2009

FROM: Robert Wesley, Bioresearch Monitoring Branch, HFM-664
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality

THROUGH: Patricia A. Holobaugh
Bioresearch Monitoring Branch Chief, HFM-664

TO: Anissa Cheung, M.D., Committee Chair, HFM-445
Bernard McWatters, Ph.D., Regulatory Project Manager, HFM 478

SUBJECT: Bioresearch Monitoring Final Review memo
STN: BLA 125297/0
Sponsor: Novartis Vaccines and Diagnostics, S.r.1.
Product: Agrippal™

SUMMARY STATEMENT

Results of bioresearch monitoring inspections of two clinical sites revealed that subjects did not receive a detailed physical exam as required by the protocol. Additionally, 51 subjects were enrolled and vaccinated at an unauthorized location.

BACKGROUND

Inspections of one clinical investigator (responsible for two clinical sites) were performed in support of this Biologics License Application (BLA). Information from the BLA was compared to source documents during the inspections. The inspections focused on specific questions concerning the pivotal study.

PROTOCOL: V71P6

STUDY TITLE: A Phase III, Randomized, Controlled, Observer-Blind, Single-Center Study to Evaluate the Consistency of Three Consecutive Lots of a Trivalent Subunit Influenza Vaccine Produced In Embryonated Hen Eggs in Healthy Subjects Aged 18 to 49 Years

Study Site		Location	FDA 483	Preliminary Classification
10	Hospital Maternidad Nuestra Senora de la Altagracia	Gazcue, Santo Domingo, Republica Dominicana	Yes	VAI
11	Centro Sanitario de Santo Domingo	Gazcue, Santo Domingo, Republica Dominicana	Yes	VAI

VAI = Voluntary Action Indicated

INSPECTIONAL FINDINGS

Site 10

- 832 subjects were screened; 826 subjects were vaccinated; 24 of the 826 were enrolled and vaccinated at a site not listed on 1572. Two subjects withdrew their consent before vaccination.
- 4 subjects had a pre-vaccination positive pregnancy test
- 765 subjects completed visit 2, and 714 subjects completed visit 3.

Site 11

- 675 subjects were screened; 667 subjects were vaccinated; 27 of the 667 were enrolled and vaccinated at the site not listed on 1572.
- 8 subjects did not meet inclusion/exclusion criteria: 3 subjects had pre-vaccination positive pregnancy tests, 3 subjects had been vaccinated with meningococcal or tetanus vaccine and were not eligible, 1 subject did not want to continue using a contraceptive method, and 1 subject was sent to collect her urine for the pregnancy test and never returned.
- 644 subjects completed visit 2, and 636 subjects completed visit 3.

For both sites, there was no evidence of under-reporting of adverse events. All protocol deviations were reported to the sponsor and were noted in the case report forms (CRFs), and there were no discrepancies noted between the source documents, CRF's, and the data submitted in the BLA.

An FDA-483 was issued to each site for the following issues.

- 51 subjects (27 subjects at Site #11 and 24 at Site #10) were enrolled at a study site not listed on the Form FDA 1572.
- Physical examinations used to assess eligibility were performed inconsistently and not always performed according to protocol. For example, abdominal exams were performed with the subjects sitting in a chair, an otoscope was not used to examine ears, and some subjects had blood pressure measurments taken only they had a history of hypertension. One sub-investigator took blood pressures only if subjects were over 30 years old, and another, only if subjects were over 40.
- Axillary temperature measurement was to be performed at visit #2 – this measurement was not performed for any subject at these sites.
- Source documents lacked information sufficient in detail to determine if the required physical examinations were performed for each study subject.

SPONSOR ISSUES

CBER was notified on September 22, 2008 that there were problems with the oversight of the study sites for Study V71P6 by the local ethics committee. Specific problems cited by the sponsor were as follows.

- Original documents, including protocol amendments, informed consents, and serious adverse event reports, were destroyed.
- The head of the Ethics Committee was unaware of the procedures and policies of the Ethics Committee.
- There is no record of the Ethics Committee review of the second protocol amendment; there is an approval letter for this amendment.
- There are discrepancies in dates and in participating members on Ethics Committee documents.
- Serious adverse event reports were sent to the Ethics Committee on a monthly basis instead of within five days as outlined in the study protocol.
- There is no documentation of the qualifications and credentials of Ethics Committee members.

The sponsor explained that none of these issues negatively impacted the human subject protection. In addition, there was a second, national Institutional Review Board monitoring the study, CONABIOS. The sponsor is not aware of any problems with oversight by CONABIOS.

In a telephone conference on September 23, 2008, the sponsor also stated that they did not have any specific doubts concerning the integrity of the study data. The sponsor stated that the study sites had been routinely monitored.

While preparing for the FDA inspection of these sites, the sponsor notified CBER a second time on February 25, 2009 that there were problems with the oversight of the study sites for Study V71P6. Specific problems cited by the sponsor were as follows:

- Enrollment and vaccination of 51 study subjects at an unauthorized off-site location different from the two authorized sites listed on the Form FDA 1572. This unauthorized site was selected independently by the Investigator and was not approved by Novartis Vaccines based on documentation in the Trial Master File.

- There was no detailed examination of body systems on the subjects seen at the unauthorized off-site location as required by the protocol. Instead, physical measurements were taken and subjects were asked about their health, as confirmed through interview with the clinical investigator.

The sponsor states that the objective of this study (V71P6) was to demonstrate consistency in immunogenicity of three consecutive lots of Agrippal™. Immunogenicity results do not change when the sponsor removed the data from these 51 from their analyses.

BIMO ADMINISTRATIVE FOLLOW-UP

Correspondence will be issued to Study Site # 10 and Study Site # 11 after complete review of the establishment inspection reports and final classification.

Should you have any questions or comments about the contents of this memorandum or any aspect of Bioresearch Monitoring, please contact me at (301) 827-6348.

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Robert Wesley
Consumer Safety Officer

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HFM-664	Access/Chron

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