DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

Certified-Return Receipt Requested

Warning Letter

JUL 12 1995

Gary Overturf, M.D.
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Albuquerque, New Mexico 87131-5311

Dear Dr. Overturf:

During the period from February 28 through March 21, 1995, Ms. Elvia Lopez, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study of an investigational vaccine in support of a product license application. This inspection is a part of FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational drugs.

We have reviewed your letter dated March 27, 1995, in which you responded to the FDA Form 483 issued to you at the end of the inspection. Although your responses adequately explain the source of some of the deviations and describe your corrective actions, we have the following comments about the deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312].

1. **Failure to promptly report serious adverse events to the sponsor.**
**[ 21 CFR 312.64(b) ]**

The protocol states, "adverse events will be looked for throughout the entire study and such events will be recorded at each examination on the clinical data sheets...any serious or alarming experiences...which occurs to any patient or subject entered into treatment in this study...whether or not related to the investigational drug must be reported immediately...". The protocol defines a serious adverse event to include one that results in patient hospitalization, prolongs an existing hospitalization, or is life-threatening.

a. Subject . was hospitalized for suspected meningitis and a seizure disorder 17 days after the first injection of investigational vaccine. This information was omitted from the adverse event (hereafter, "AE") form for this period. A follow-up AE report for this injection describes the incident and was prepared by the sponsor's representatives in February, 1995, approximately 2.5 years following the event.

b. You failed to report the following hospitalizations to the sponsor in a timely manner on the appropriate case report forms:

i. Subjects were hospitalized with conditions unrelated to the study. We note from your response letter that you will notify the sponsor of these events.

ii. The sponsor's representatives prepared reports to notify the sponsor of the hospitalizations of Subjects during a site visit.

2. **Failure to ensure that an investigation is conducted according to the signed investigational plan (protocol). [ 21 CFR § 312.60 ]**

a. Subjects were administered non-study Haemophilus vaccine, and were subsequently administered an additional dose of study vaccine and underwent study-related blood sampling.

b. The protocol states that the nurse or investigator will contact the parent or guardian approximately 24 hours after each vaccination. This safety assessment was not conducted for several subjects, and is especially important in a subject population in which one would anticipate a low rate of return of the 14 day adverse reaction diaries. The following examples are illustrative: (injections 1 and 2), (injections 2 and 3), (injection 2), (injections 2 and 3), and (injections 1, 2, and 3).

We recognize that it may be difficult to reach the parent or guardian to obtain this information. Your attempts to contact the subjects' families should be documented in the case report forms.

c. The protocol states that, "all adverse reactions which occur within 14 days following each injection of vaccine must be recorded in detail on each subject's case report form." In many cases this safety assessment was not conducted until several weeks after the vaccination occurred. You should document in the case report forms your attempts to contact the subjects' families. Examples include, but are not limited to, the following:

| subject | injection | injection date | safety assessment date |
|---|---|---|---|
| | 2 | June 3, 1992 | Aug. 4, 1992 |
| | 3 | Feb. 18, 1993 | April 13, 1993 |
| | 3 | Feb. 22, 1993 | April 13, 1993 |
| | 2 | Sept. 1, 1992 | March 1, 1993 |
| | 2 | Oct. 27, 1992 | Feb. 24, 1993 |

v. Adverse reactions listed on the parent report card were not transferred to TT form for the third injection of subject .

vi. The duration of adverse reactions recorded on the TT form for first injection of subject were not recorded on the AE form. The information provided on the revised form (revision date January 8, 1993) is not documented as to its source.

vii. The AE form for subject did not report fever and fussiness two days following the third injection, or include physician's assessment of sinusitis, sty, risk for anemia, and viral stomatitis.

b. Typed case reports do not always accurately reflect the information in the handwritten worksheets. The handwritten worksheets are considered to be source data because information is recorded here from telephone contacts, etc. The typed pages should accurately reflect information documented on the handwritten sheets. For example:

i. The handwritten TT worksheet for the second injection of subject states, "currently being tx for O.M. - no fever on amoxicillin since 6/10/92". This information is missing from the typed page sent to the sponsor.

ii. The report card (hereafter, "RC") for the second injection of subject does not report erythema at the injection site as reported on the handwritten copy of the TT sheet.

iii. There are discrepancies between the information on the RC page completed by the parent for the second injection of subject and the TT and AE sheets completed by your staff.

iv. There are discrepancies in the information between the handwritten and typed TT sheets for the second injection of subject .

v. The typed version of TT for second injection of does not capture all information related to high-pitched crying and other reactions noted on handwritten sheet.

c. Some case report forms were "corrected" several months after the original entries, with no documentation to indicate the reason for the change or source documents to justify the changes. Examples of documents changed on January 8, 1993, include, but are not limited to, the following: