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

CBER-00-001

OCT 8 1999

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Wayne Morges, Ph.D.
Vice President for Quality and Regulatory Affairs
North American Vaccine, Inc.
12040 Indian Creek Court
Beltsville, MD 20705

Dear Dr. Morges:

The Food and Drug Administration (FDA) conducted an inspection of North American Vaccine, Inc., located at 12040 Indian Creek Court, Beltsville, MD, between June 1, 1999, and July 2, 1999. During the inspection, FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and deviations from the applicable standards and requirements of Subchapter C Parts 210 and 211, and Subchapter F Parts 600-680, Title 21, Code of Federal Regulations (21 CFR). The deviations noted on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection include, but are not limited to the following:

1. Failure to establish and/or follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product, and to test and approve, or reject in-process material at the commencement or completion of significant stages of the production process to assure that drug product and in-process material conform to specifications [21 CFR 211.110]. For example:
 - a. Pertussis Toxoid batches 300173 and 300175 did not meet in-process acceptance criteria for the Histamine Sensitization Factor Assay (HSA) test as per Standard Operating Procedure (SOP) 21T12 entitled "Histamine Sensitization Factor Assay," however, both batches were released and used to formulate final product

- e. No investigation was conducted after [redacted] of [redacted] ELISA assays for Acellular Pertussis potency testing of lot 400026 were found invalid.
3. Failure to maintain and follow an appropriate written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166]. For example:
 - a. SOP 21T35 entitled "[redacted]" was not followed in that:
 - i. Diphtheria and Tetanus potency testing of Lot C009 at the 0 month time point produced invalid and failed results [redacted].
 - ii. Lot B002 failed Diphtheria potency testing at the 18 month time point. Retesting could not occur as appropriate because [redacted].
 - iii. The SOP allows for [redacted].
 - b. Stability data are not available for the following time points:
 - i. Lot C009 did not have test results for Diphtheria and Tetanus potency and for Percent Diphtheria and Percent Tetanus Adsorption at 0 months.
 - ii. Lot C009 did not have test results for Acellular Pertussis potency and HSA at 3 months.
 - iii. Lot C010 did not have test results for Percent Diphtheria and Percent Tetanus Adsorption at 0 and 3 months.
 4. Failure to establish and/or follow adequate written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100]. For example:
 - a. SOPs do not describe the requirements for mixing of the sample of adsorbed Pertussis Toxoid intermediates, bulk product, or final filled container prior to

removing an aliquot for pH testing. Percent adsorption, thimerosal, and aluminum testing is also performed on the aliquot, for which lack of mixing could affect the test results.

- b. The disinfectant [redacted] was replaced by [redacted] as a cleaning agent in September 1998, however, [redacted] was used to clean [redacted] Laminar Air Flow unit 3707 in April 1999.
 - c. Planned deviations to SOPs for QC testing are not routinely kept with the SOP nor are the planned deviations routinely issued with the test records.
 - d. A planned deviation for a potency test in May 1999 that modified the test procedure was not referenced in the test record until June 1999.
 - e. SOP 21T69 entitled "[redacted]" is inadequate in that there is no requirement for documentation of review of sample results and of the final interpretation of test results. In addition, no pass/fail determination of the test result is made.
 - f. Identifications of microbial isolates were not available for microbial testing failures on March 3, 1999, and April 14, 1999.
 - g. Media fill procedures do not describe required activities in response to a failure.
 - h. There is no SOP for the practice of periodic removal of expired materials from storage areas.
5. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)]. For example:
- a. SOP 21T69 entitled "[redacted]" does not specify a holding time limit for a sample prior to testing.
 - b. Manufacturing operations occur 24 hours per day, 7 days a week, however the Water for Injection (WFI) system is only monitored Monday through Friday.
 - c. New lots of Chinese Hamster Ovary (CHO) cells used in the assay to quantitate active toxin before and after inactivation are not qualified prior to use.

Section VI.A.2. of the SOP includes the statement, "[REDACTED]"

4Aii. We have reviewed SOP 3MM94 entitled "Procedure for Investigation of Out of Specification Results on the Water System" that was submitted in support of your corrective action and note that the SOP defines an alert level as "[REDACTED]" and defines an action limit as "[REDACTED]". We believe

that alert limits and action limits should not be defined as the frequency of excursions from acceptable specifications, but as numerical specifications. For example, the microbial specification for WFI is defined by USP as 10 cfu/100 ml, which is routinely used by firms as the action limit. An alert limit is routinely lower, to provide an indication that a problem may be developing in the water system requiring increased vigilance.

10. Your response indicates that investigations of out of specification microbial testing will include comparison of Gram staining and colony morphology of the out of specification result with any other bacterial colonies isolated on that sample date. Our review of SOP 3MM94 entitled "Procedure for Investigation of Out of Specification Results on the Water System" that was submitted in support of your corrective action did not note this requirement.
11. Your response indicates that SOP 3MM64 entitled "Review of Manufacturing Batch Records - Review Checklist" has been revised to ensure that WFI monitoring data is reviewed prior to release of product, however, our review of the SOP that was submitted in support of your corrective action did not note this requirement.
13. We note your commitment to revise your SOP to require immunization of [REDACTED] of animals at each time point. Please explain whether this practice will be limited to stability samples or incorporated into your routine testing program. In addition, your response does not address the steps you will take to ensure the revised SOP is appropriately followed. This inspectional observation demonstrated that the SOP in use at the time of the inspection was not followed.
16. We agree that any ambiguity in the SOP related to repeat testing should be clarified. The SOP revisions should clearly define valid, invalid, and failing test results and ensure that the actions to be taken in the event of invalid and failing results are scientifically sound.
18. The data from the studies conducted that demonstrate the comparability of the assay when performed at your firm should be submitted to the license application. In addition, we request that you provide the cover letter of that submission as response to this letter.

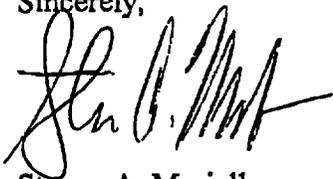
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be exported under Section 802 of the FD&C Act if such drug is not manufactured, processed, packaged or held in substantial conformity with the CGMP requirements.

Please notify this office in writing, within 15 working days of receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, injunction, license suspension, and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610.

Sincerely,

A handwritten signature in black ink, appearing to read "Steven A. Masiello". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and
Research