DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

MAY 11 2006

Certified Mail
Return Receipt Requested

Reference No: 06-HFD-45-0501

Jeffrey A. Blair
President and Chief Executive Officer
North American Science Associates, Inc.
6750 Wales Road
Northwood, OH 43619-1397

Dear Mr. Blair:

Between April 11 and May 9, 2005, Hugh M. McClure III, representing the Food and Drug Administration (FDA), inspected the following nonclinical laboratory studies conducted by your firm:

Protocol [ ] entitled "Chronic Toxicity Study of [ ] Delivery System Implanted Subcutaneously in Dogs (Pilot Report)," performed for [ ]

Protocol [ ] (same as above), entitled "Chronic Toxicity Study of [ ] Delivery System Implanted Subcutaneously for 10 Months in Dogs," performed for [ ]

Mr. McClure also inspected other studies under evaluation by FDA's Center for Devices and Radiological Health. This letter addresses only the second study cited above.

This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to verify compliance with Title 21 of the Code of Federal Regulations (CFR), Part 58 -- Good Laboratory Practice (GLP) regulations. The regulations at 21 CFR Part 58 apply to nonclinical laboratory studies of products regulated by FDA.

At the conclusion of the inspection, Mr. McClure presented and discussed the items listed on Form FDA 483, Inspectional Observations. Following our review of the establishment inspection report and related documents, including your letter dated May 18, 2005, we conclude that you violated FDA regulations governing the conduct of nonclinical laboratory studies. This letter provides you with written notice of the violations. The applicable provisions of the CFR are cited for each violation.

**1. Your study director failed to assure that the protocol, including any changes, was followed, and that all experimental data were accurately recorded and verified. [21 CFR 58.33 (a, b) and 21 CRF 58.130 (a, e)]**

The protocol required that each dog in test groups A1, A2, B1, and B2 be implanted with either 24 test article (delivering controlled-release [ ] or 24 control rods. Study records fail to document the number of test article or control article rods implanted in each dog. In your May 18, 2005 response to the Form FDA 483, you acknowledged that the implant procedure records do not document the number of control or test article rods actually implanted. While FDA recognizes that the protocol specifies the number of rods to be implanted, and your response states that the protocol was adhered to, it is important to document the actual number of rods inserted in each animal to help assure that the protocol was in fact followed. Study records also do not document the specific lot of test article (5 lots were used) administered to each animal and, consequently, characterization information for those lots cannot be linked to specific animals. Because you failed to document the number of rods inserted into, or identify the lot of test article administered to, each animal, the dose of [ ] delivered to the test animals cannot be assured per the protocol. Thus, no conclusions can be drawn from this study.

**2. The final report did not identify the test article by strength, purity, and other appropriate characteristics. [21 CFR 58.185 (a)(4)]**

The study records indicate that five lots (batches) of test article [ ] were used during the study. However, the final report dated September 23, 2002 indicated, incorrectly, that only lot [ ] was used. In response to the Form FDA 483 inspectional findings, the study director amended the final report on May 18, 2005 to acknowledge that three additional lots [ ] were used in the study. The amended report still did not mention use of lot [ ] The final study report and the amended report failed to include the required characterization information (e.g., strength, purity) for any lot of the test article used.

**3. The final report for the study did not include a description of all circumstances that may have affected the quality or integrity of the data. [21 CFR 58.185 (a)(9)]**

The final study report failed to include the occurrence of elevated body temperatures experienced by some study animals and the potential implications for study data. The 6 month, 9 month, and termination physical examination records indicated that several study animals had elevated body temperatures ranging from 103.1 to 107.1°F (normal body temperature for [ ] dogs is approximately 102°F). The elevated body temperatures could have resulted from exposure to the study drug, among other things, and may have affected the pharmacokinetics and pharmacodynamics of [ ] in the test animals and thus affected the quality of the study data. The examination records only state "AN" or "Appeared Normal." There is no documentation to indicate that the study director investigated either the cause or possible effects

of the elevated body temperatures on the integrity of the study data.

4. **You failed to retain reserve samples for each batch of test and control articles for studies more than 4 weeks long. [21 CFR 58.105(d)]**

Specifically, you did not retain reserve samples for test article lots #[ ] and control article lot [ ]

5. **Your study director did not have overall responsibility for the technical conduct of the study, as well as for interpretation, analysis, documentation, and reporting of results, and she was not the single point of study control. [21 CFR 58.33]**

The approved protocol dated July 9, 2001, stated that animals designated for 9 month termination would be re-implanted with test article rods at 6 months or when levels of [ ] had dropped to 80% of the initial steady state values, whichever came first. The protocol also stated that re-implantation would be on the left side of the chest/back and that the original implants on the right side of the chest/back would be removed at the time of re-implantation. The sponsor changed the procedure on March 21, 2002 so that re-implantation would be based solely on the blood levels of [ ] and the original implants on the right side would remain in place. However, the study director never saw the pharmacokinetic data needed for her to determine whether blood levels met the criteria for re-implantation. She merely followed the sponsor's instructions to implant the rods based on pharmacokinetic data in the possession of the sponsor. For the study director to fulfill her responsibility as the single point of study control, she should have reviewed the actual pharmacokinetic data to determine when to implant the additional rods. The study director also failed to document these changes to the protocol until August 15, 2002, five months after the re-implantations procedure was performed.

6. **The signed and dated reports of each of the individual scientists or other professionals involved in the study were not included in the final report. [21 CFR 58.33, 58.185 (a)(12)]**

The final study report must include the signed and dated reports of each of the individual scientists or other professionals involved in the study. The study report did not contain the pharmacokinetic data and analyses, did not address why they were missing, and did not identify the scientist or other professionals involved in that portion of the study.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. Your violation of the FDA regulations outlined above resulted in the submission of unreliable data to the sponsor, and the submission of unacceptable data to FDA. Your response dated May 18, 2005 addressed some of these deficiencies, however, your response did not provide adequate assurance that you have established policies and procedures to prevent recurrence of the violations cited above. You must correct the deficiencies noted above and establish procedures to ensure that any on-going or future studies will be conducted in compliance with FDA

regulations.

Within fifteen (15) working days of receipt of this letter, you must notify this office in writing of the specific corrective actions you will take to address all of the deficiencies noted above and to achieve compliance with the FDA regulations. If corrective actions cannot be completed within 15 working days, you may request an extension of time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether it is adequate. Failure to provide adequate assurances of compliance with FDA regulations may result in further regulatory action without further notice.

Your reply should be sent to:

C.T. Viswanathan, Ph.D.
Associate Director, Bioequivalence
Chief, GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 116
Rockville, MD 20855
Telephone: (301) 827-5460

Sincerely,

Joseph P. Salewski

Joseph P. Salewski
Acting Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research