DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 240-453-8298
FAX: 240-453-6909
E-mail: patrick.mcneilly@hhs.gov

August 29, 2006

Sharon L. Tennstedt, Ph.D.
Vice President
Director, Center for Scientific Integrity
New England Research Institutes, Inc.
9 Galen Street
Watertown, MA 02472

RE: Human Research Subject Protections Under Federalwide Assurance FWA-297

Research Project:	**Health Effects of Dental Amalgams in Children**
Principal Investigator:	**Dr. Sonja M. McKinlay**
HHS Project Number:	**5U01DE011886**

Dear Dr. Tennstedt:

The Office for Human Research Protections (OHRP) has reviewed the New England Research Institute's (NERI) September 1, 2005 report that was submitted in response to OHRP's July 25, 2005 letter regarding the above-referenced research.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) It was alleged that researchers in the above-referenced research failed to minimize risks to subjects, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1). In specific it was alleged that the research continued despite new scientific findings that emphasized the potential for harm from doses of mercury within the range of that received by the general population from amalgam fillings. OHRP finds that this allegation could not be substantiated. In particular, OHRP notes that the interventions utilized in the research involved standard materials and techniques used in dental restorations. In addition, the study was reviewed by a Data Safety and Monitoring Board which apparently did not identify any new scientific findings related to potential harm to subjects or question the continuation of the study.

(2) It was alleged that the enrollment procedures for the above-referenced research failed to minimize the possibility of coercion or undue influence, as required by HHS regulations at 45 CFR 46.116. In specific, it was alleged that the language regarding the availability of alternatives and the risks associated with them were coercive. In addition, it was alleged that the compensation paid to subjects was coercive.

OHRP finds that these allegations could not be substantiated. In particular, OHRP notes that the IRB-approved informed consent document states:

> (a) "Because mercury in large amounts can cause health problems, scientists have wondered whether the very small amounts of mercury from dental amalgam and even from food, water and air can also cause some of these problems. High levels of mercury can cause tremors, loss of memory, insomnia, fatigue, headaches, irritability, slowed nerve conduction, appetite loss, and kidney problems."
>
> (b) "My child has a 50% chance of being in the amalgam group, with the risk of low level mercury exposure. Dental amalgam, however, is currently the most frequently used material to fill cavities in back teeth, and if I choose to not participate in this study, it is very likely that my child's teeth will be filled with amalgam by another dentist."
>
> (c) "If my child is in the non-amalgam group, the tooth-colored dental composite, on rare occasion, may cause an allergic reaction in the lining of the mouth. Also sometimes, the dental composite releases a chemical in the mouth that in much larger amounts may cause cancer. However, this filling material is currently the standard material used to fill cavities in the front teeth and many back teeth."

In addition, OHRP notes that the subjects were to receive between $20 and $50 per clinic visit to cover the costs of transportation and the completion of neuropsychological testing.

(3) It was alleged that the informed consent document for the above-referenced research failed to include an appropriate description of any benefits to the subjects or to others that may reasonably be expected from the research, as required by HHS regulations at 45 CFR 46.116(a)(3). In specific, it was alleged that the benefits of the research may be overstated.

OHRP finds that this allegation could not be substantiated. In particular, OHRP notes that regarding the benefits of the research, the IRB-approved informed consent document states:

> (a) "A major benefit of my child's participation in this study is that he/she will

receive high-quality comprehensive dental care for 5 years"

(b) "The blood tests will also provide information about my child's blood iron and lead levels: this is an opportunity to identify possible lead exposure."

(c) "In addition, I realize that information from this study may lead to advances in dental and medical knowledge."

OHRP acknowledges that in response to the current investigation, NERI has required all investigators and research staff to complete protection of human subjects training every two years. In addition, the NERI IRB has reviewed and revised its standard operating procedures regarding (i) back translation of informed consent documents; (ii) review and approval of informed consent documents and recruitment material in multi-site studies; and (iii) determination of studies eligible for expedited review.

At this time, OHRP has the following additional question:

[Redacted]

Please provide your response to the above question no later than October 6, 2006.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Nancy Gee, IRB Administrator, NERI
Dr. Donald Brambilla, Chair, Institutional Review Board, NERI
Commissioner, FDA
Dr. David Lepay, FDA

Dr. Norris Alderson, FDA
Dr. Sam Shekar, NIH
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Dr. Kristina Borror, OHRP
Dr. Irene Stith-Coleman, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Carla Brown, OHRP