DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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November 14, 2002

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President
Loma Linda University
Loma Linda, CA 92350

Barry L. Taylor, Ph.D.
Vice President for Research Affairs
Loma Linda University
Loma Linda, CA 92350

Zareh Sarrafian, M.B.A.
Chief Executive Officer
Loma Linda University Behavioral Medicine Center
1710 Barton Road
Redlands, CA 92373

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1295
Research Project: Double-Blind, Randomized, Placebo-Controlled Long-Term Low Dose Perchlorate Exposure Study
Protocol Number: 799735
Principal Investigator: Anthony Firek, M.D.

Dear Mr. Behrens, Dr. Taylor and Mr. Sarrafian:

The Office for Human Research Protections (OHRP) has reviewed the Loma Linda University's (LLU) report dated July 12, 2002 that was submitted in response to OHRP's May 16, 2002 letter regarding

the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above-referenced research.

Based upon its review of LLU's July 12, 2002 report, OHRP makes the following determinations regarding the above-referenced research project:

(1) HHS regulations at 45 CFR 46.116(a)(1) require that informed consent include, among other things, an explanation of the purpose of the research and a complete description of the procedures to be followed and identification of any procedures which are experimental. OHRP finds that the informed consent document approved by the LLU Institutional Review Board (IRB) failed to include an accurate explanation of the purpose of the research and an accurate description of how the maximum level of perchlorate exposure during the study would compare to maximal exposure expected from drinking contaminated drinking water seen in California or other regions of the country.

Furthermore, it appears that the LLU IRB failed to identify and resolve substantive discrepancies in documents presented by the investigators regarding the level of perchlorate to which subjects were to be exposed relative to the maximal level of exposure expected from drinking contaminated drinking water seen in California.

In particular, OHRP notes the following:

(a) The Purpose of the Study section in the LLU IRB-approved informed consent document for the research protocol stated the following:

> "Recently, Perchlorate has been found in very small amounts in the drinking water of certain communities in California, Nevada, and Arizona. This research study will investigate whether very small amounts of Perchlorate, such as encountered in ground water contamination, may change thyroid tests."

(b) The IRB-approved informed consent document does not compare the daily doses of 0.5, 1, or 3 mg of perchlorate to the maximal exposure that would be expected from drinking contaminated water in California or other regions of the country.

(c) The research protocol stated the following:

(i) "Concentrations in wells in California have exceeded 18 µg/L, with a maximum concentration of 280 µg/L detected in one public drinking water system[2] (USEPA, 1998). [[2] It should be noted that there is no evidence that anyone has consumed drinking water with a perchlorate concentration of 280µ/L. This is because the maximally contaminated well was interconnected with other wells with lower perchlorate concentrations of perchlorate, such that mixing and dilution would have occurred prior to consumption.]"

(ii) "At California's current drinking water action level of 18 µg/L, people could be exposed to a perchlorate dose of 36 µg/day, assuming a drinking water ingestion rate of 2 liters per day. At the maximum perchlorate concentration detected in a public drinking water system (280 µg/L), people could be exposed to a perchlorate dose of 560 µg/day."

(iii) "**It should be noted that 3 mg per day is approximately 5 fold greater than the theoretical maximum dose of perchlorate which people in California may have received *via* drinking water ingestion, as discussed above.**" [emphasis added]

(iv) "Perchlorate doses of 1 and 3 mg/day are approximately 30 and 100 fold, respectively, greater than the dose associated with ingestion of drinking water at current drinking water guidelines for perchlorate."

(d) The LLU IRB March 8, 2000 Meeting Minutes at which the research protocol was initially approved stated the following:

"This study will investigate whether very small amounts of perchlorate, such as encountered in the drinking water of certain communities in California, Nevada and Arizona from ground water contamination, may affect the way the thyroid gland works."

(e) The December 20, 2000 letter from Dr. Firek to the LLU IRB Chairman in response to LLU IRB's letter of December 5, 2000 regarding required modifications to the research protocol stated the following:

"Our group designed the study based on three risk-benefit premises, 1) the

> dosage of Perchlorate could be no higher than levels reported historically in contaminated water supplies. This allowed us to use the EPA, State of California and published epidemiological databases in affixing risk."

The LLU IRB subsequently approved the modifications to the research protocol without noting that this statement directly contradicts the information presented in the initially approved protocol cited in (c) above.

(f) LLU's July 12, 2002 report stated the following:

> "OHRP references the Outline of Previous Perchlorate Exposure Studies and Rationale for the Loma Linda Study (identified as Appendix A in our original response). Appendix A was developed by the on-site Principal Investigator as an executive summary for internal use during the preparations of LLU's previous response to Office of Human Research Protections (OHRP) questions regarding the IRB's review of this study. The investigator provided this document as background and historical context for the institutional officials participating in this effort, who were not involved in the initial review of this study. We provided Appendix A to OHRP as 'information about other perchlorate exposure studies that we found useful in answering inquiries from the press and special interest groups.'
>
> This document was not used by the Institutional Review Board (IRB) during the initial or continuing review of the study.
>
> The statement that the 'highest dose of perchlorate (3mg/day) exposure could be no higher than doses historically received by people in contaminated areas based on levels detected in drinking water supplies' is not in agreement with the protocol and was not a consideration used in the review of the study. The committee was aware that the maximum study exposure dose was 'approximately 5 fold greater that the theoretical maximum dose of perchlorate which people in California may have received via drinking water ingestion."

(2) HHS regulations at 45 CFR 46.111(a)(1) require that in order to approve research, the IRB shall determine that the risks to subjects are minimized by using procedures which are

consistent with sound research design. OHRP finds that the LLU IRB failed to ensure that this requirement was satisfied when it approved the above-referenced research. In particular, OHRP notes the following:

(a) The research represents a toxicology study in which the effects of an environmental toxin, perchlorate, on the thyroid gland was to be measured in healthy volunteers at different doses of exposure. Risks to subjects in such a toxicology study would have been more effectively minimized by exposing sequential groups of subjects to progressively increasing levels of environmentally relevant doses of perchlorate based upon dose-response assessments, rather than randomly assigning subjects to various dosage levels of perchlorate as was done per the IRB-approved protocol.

(b) The Sponsor's objective section in LLU's previous July 12, 2001 report stated the following:

> "The primary sponsor objective is to determine if six month, low dose exposure to perchlorate will affect thyroid function in healthy adults. The results should be successful in defining a no effect level of perchlorate for 6-month exposure. The lack of carefully controlled human experiments testing both the threshold level and dose duration effects of perchlorate on thyroid gland regulation has prevented establishment of permanent water standards for perchlorate. More importantly, both physicians and exposed residents are unsure about the health consequences of perchlorate exposure.
>
> The study conducted in Loma Linda is unique and differs from other human perchlorate trials in a number of ways. Single daily dosing exposure carried out over a six-month period may better approximate real life perchlorate exposure. The study will potentially reveal an important dose duration effect. In addition, the study is potentially useful to the EPA [United States Environmental Protection Agency] in considering new monitoring standards for water clean up."

(c) OHRP notes that the Health Effects/Toxicology section in a discussion paper

regarding perchlorate contamination published on EPA's Office of Ground Water and Drinking Water web site (copy enclosed) stated the following:

> "The currently available database on the health effects and toxicology of perchlorate or its salts is very limited. The majority of human data are clinical reports of patients treated with potassium perchlorate for hyperthyroidism resulting from an autoimmune condition known as Grave's disease. Potassium perchlorate is still used diagnostically to test thyroid hormone [thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) production in some clinical settings. The basis for the effect on thyroid hormone function is the competitive inhibition of iodide anion uptake into the thyroid gland by perchlorate anion (ClO_4) which then results in reduced thyroid hormone production.
>
> It is difficult to establish a dose-response for the effects on thyroid function from daily or repeated exposures in normal humans from the data on patients with Grave's disease because of a variety of confounding factors, including: the effect of the disease, that often only a single exposure and not repeated exposures were tested, that only one or two doses were employed, and that often the only effect monitored was iodine release from the thyroid or control of the hyperthyroid state. There are limited data in normal human subjects and laboratory animals that support the effect of perchlorate on thyroid hormones, but the majority of these additional studies suffer from the same limitations with respect to the number of doses and exposures. These limitations prevent the establishment of a quantitative dose-response estimate for the effects on thyroid hormones after long-term repeated exposures to perchlorate in healthy human subjects."

(3) OHRP noted that the above-referenced research was revised to add a 0.5 mg/day exposure group with a concomitant increase in study enrollment from 75 to 100 subjects.

LLU's July 12, 2002 report stated the following in response:

> "As mentioned above, the interpretation of the amendment to add a third group of 0.5 mg/day as being a minor change was based on the initial IRB determination that the risk to the higher levels of exposure was minimal risk. Any guidance on additional objective

criteria, above those previously published, to classify changes as greater than 'minor' would be appreciated."

HHS regulations at 45 CFR 46.110(b)(2) allow for expedited review for minor changes in previously approved research during the period for which approval is authorized. OHRP finds that the protocol amendments to add a new exposure group and to increase the number of subjects exceeded the limit of minor changes to the originally approved research and was not in accordance with HHS regulations at 45 CFR 46.110(b)(2).

Required Action: By January 3, 2002, LLU must submit to OHRP a satisfactory corrective action plan to address findings (1) - (3) above. In developing its corrective action plan for finding (1), LLU should determine whether previously enrolled subjects should be contacted and provided with additional information regarding the dose of perchlorate exposure relative to the maximal exposure that would be expected from drinking contaminated water in California or other regions of the country.

OHRP finds that LLU has adequately responded to the other questions and concerns stated in OHRP's May 16, 2002 letter.

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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

Enclosure

cc (w/enclosure): Dr. Richard H. Hart, Chancellor & CEO, LLU
Dr. G. William Saukel, Chair, LLU IRB

cc: Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. John Mather, ORCA, DVA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
Mr. George Gasparis, OHRP
Dr. Kamal K. Mittal, OHRP
Mr. Barry Bowman, OHRP