DEPARTMENT OF HEALTH & HUMAN SERVICES

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August 31, 2001

Walter W. Noce, Jr.
President and Chief Executive Officer
Childrens Hospital Los Angeles
4650 Sunset Blvd., Mailstop #1
Los Angeles, California 90027

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1118

Research Activity: Genetic study of individuals with Ectopia Lentis et Pupillae and their family members living in an Iranian village
Principal Investigator: Dr. J. Timothy Stout

Dear Dr. Noce:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed your July 25, 2000 report regarding the above-referenced research that was submitted in response to OPRR's May 11, 2000 letter.

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

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(a) and the Childrens Hospital Los Angeles (CHLA) MPA (see Part 1, section II.B) require that all research involving human subjects that is not exempt under HHS regulations at 45 CFR 46.101(b) be reviewed and approved by the CHLA Institutional Review Board (IRB).

OHRP finds that the investigators failed to obtain IRB approval for the research which involved obtaining blood samples from members of an Iranian village in order to determine the genetic basis for Ectopia Lentis et Pupillae. As a result, CHLA failed to ensure that the research satisfied the criteria for IRB approval stipulated by HHS regulations at 45 CFR 46.111.

(2) HHS regulations at 45 CFR 46.116(a) stipulate the basic elements required for obtaining the legally effective informed consent of subjects. OHRP acknowledges that the investigators obtained and documented the consent of the subjects using a consent form that described the purpose of the research and the basic study procedures to be followed.

However, OHRP finds that the informed consent document used by the investigators failed to include an adequate description of the basic elements of informed consent stipulated by HHS regulations at 45 CFR 46.116(a)(2), (4), (6), (7), and (8). Furthermore, OHRP finds that the informed consent document appeared to include complex language and concepts that would not have been understandable to all subjects.

Corrective Actions: OHRP acknowledges that CHLA has taken or proposed the following corrective actions in response to the above findings:

(1) The principal investigator has been notified that DNA samples obtained during the conduct of the above-referenced research cannot be analyzed further and the results cannot be published.

(2) CHLA has implemented a requirement that all investigators and other appropriate personnel take an educational course on the relevant regulations and ethical principles related to human subject research.

(3) CHLA has expanded the administrative staff supporting the CHLA IRB.

(4) CHLA has developed and implemented a new policy regarding protection of human subjects in international research.

(5) CHLA is attempting to recruit additional IRB members with particular attention to ethnicity and cultural diversity of its research subject population.

(6) CHLA will install a computerized database system to track and monitor human subject research protocols.

(7) An enhanced program of continuing education for all IRB members will be instituted.

(8) A system for auditing the activities of the IRB on an ongoing basis will be implemented.

OHRP has determined that these corrective actions adequately address the above findings, as well as the other concerns raised in OHRP's May 11, 2000 letter. As a result, there should be no need for further OHRP involvement in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP would like to provide the following additional feedback and guidance regarding the CHLA's minutes of IRB meetings and written IRB policies and procedures:

(1) OHRP highly commends the CHLA IRB for the detailed content of the minutes of its meetings. The minutes are indicative of a review process that is clearly substantive and meaningful and should help ensure the protection of human subjects.

(2) OHRP commends CHLA for having written IRB policies and procedures that overall are robust and very detailed.

(3) OHRP recommends that the IRB policies and procedures be expanded to include additional operational details for the following procedures:

(a) The procedures which the IRB follows for ensuring prompt reporting to the IRB of proposed changes in research, and for ensuring that such changes in approved research may not be initiated without IRB review and approval except when necessary to eliminate immediate hazards to subjects.

(b) The procedures for determining which projects require review more often than annually, and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(c) The procedures for ensuring prompt reporting to appropriate institutional officials, the head of any sponsoring federal department or agency, and OHRP (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance; and (iii) any suspension or termination of IRB approval.

(4) Regarding the "CCI POLICY ON TRANSLATION OF STUDY CONSENTS INTO NATIVE (NON-ENGLISH) LANGUAGES" on page V-44, item 2, please note that it could be appropriate for the IRB to require informed consent documents to be translated into the native language of prospective subjects when investigators intend to enroll non-English speaking subjects.

The regulations require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (see 45 CFR 46.116 and 46.117). Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language understandable to them. OHRP strongly encourages the use of this procedure whenever possible.

Alternatively, HHS regulations at 45 CFR 46.117(b)(2) permit oral presentation of informed consent information in conjunction with a short form written informed consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written informed consent document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

(5) Regarding the "GUIDELINES FOR ADOLESCENT HEALTH RESEARCH," on page VI5-7, please note that parental permission for research involving children, including adolescents, cannot be waived unless the IRB makes and documents the findings required under HHS regulations at 45 CFR 46.116(c), 46.116(d), or 46.408(c).

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,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Thomas G. Keens, Chairman, IRB, CHLA
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Dr. Kamal Mittal, OHRP
Mr. Barry Bowman, OHRP