DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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August 12, 2004

Steven Packer, M.D.
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Monterey, CA 93942

RE: General Human Research Subject Protections Under Cooperative Project Assurance (CPA) T-3900

Dear Dr. Packer:

The Office for Human Research Protections (OHRP) has reviewed the documents related to the above referenced research that were submitted with your report of February 7, 2004, in response to OHRP's letter of December 30, 2003.

The allegations involved the following:

(1) Failure to review proposed research at a convened meeting at which a majority of the institutional review board (IRB) members are present, including at least one member whose primary concerns are in nonscientific areas, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.108(b).

(2) IRB members participating in the IRB's initial or continuing review of projects in which the member has a conflicting interest, in contravention of HHS regulations at 45 CFR 46.107(e). In specific, it was alleged that the Community Hospital of the Monterey Peninsula (CHOMP) IRB Chair had voted on several proposed research protocols in which he was an investigator.

Corrective Actions: OHRP acknowledges that CHOMP has taken numerous actions to address the concerns expressed in OHRP's December 30, 2003, letter including: (a) retaining an expert consultant to assist in redesigning the CHOMP IRB administration and function; (b) establishment of new governance, operational, and compliance oversight structures for the CHOMP IRB; (c) development of educational materials and a

training program for CHOMP IRB members; (d) reconstitution of the IRB membership, including the Chair, to reduce conflict of interest and to allow for additional community participation; and (e) suspension of new accruals to open studies until further review by the new CHOMP IRB. The current version and the draft of the revised CHOMP IRB policies and procedures clearly specify that at each meeting of the full IRB, at least one non-scientist and a majority of IRB members must be present. OHRP finds that these corrective actions adequately address the allegations outlined in paragraphs (1) and (2) and are appropriate under the CHOMP assurance.

(3) Failure of the institution to have written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

> (a) The procedures which the IRB will follow for conducting its initial review of research.
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> (b) The procedures which the IRB will follow for conducting its continuing review of research.
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> (c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.
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> (d) The procedures which the IRB will follow for determining which projects require review more often than annually.
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> (e) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.
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> (f) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
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> (g) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of: (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

Corrective Actions: OHRP acknowledges that the draft of the revised CHOMP IRB policies and procedures includes a description of the procedures which the IRB will follow for determining which projects require review more often than annually; the procedures for ensuring prompt reporting to the IRB, any Department or Agency head,

and OHRP of any serious or continuing noncompliance; the procedures for ensuring prompt reporting to OHRP of any suspension or termination of IRB approval; and the procedures for ensuring prompt reporting to the IRB of adverse events.

Required Action: By September 23, 2004, please provide OHRP with written procedures, including operational details, which the IRB will follow:

(a) For conducting its initial review of research (the draft procedures do not include a description of any primary reviewer system used for initial review, but only list the requirement that documents be submitted and tell when).

(b) For conducting its continuing review of research. OHRP notes the following:

(i) The draft procedures only list the requirement that documents be submitted and tell when.

(ii) The conditions under which IRB approval of a research study must remain active do not appear to include all research activities currently involving human subjects, including analysis of identifiable private information that has already been collected.

(iii) OHRP recommends that the IRB receive a concise summary of all adverse events for continuing review, not just those that are unexpected, of moderate or greater severity, and associated with the research.

(c) For reporting its findings and actions to investigators and the institution (these procedures do appear in the current written procedures but not in the draft of the revised procedures).

(d) For determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review (such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

(e) For ensuring prompt reporting to the IRB, appropriate institutional officials, any Department or Agency head, and OHRP of any unanticipated problems involving risks to subjects or others; for ensuring prompt reporting to appropriate institutional officials any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and for ensuring prompt reporting of any suspension or termination of IRB approval to the appropriate

institutional officials and any Department or Agency head.

(f) OHRP notes that section "1.0 Compliance" of the revised draft procedures refers to "noncompliance with the National Institutes of Health human subjects regulations...." This section should refer to the HHS regulations for the protection of human subjects.

(4) Failure of the institution to prepare and maintain adequate documentation of IRB activities, as required by HHS regulations at 45 CFR 46.115(a).

(5) Failure to ensure that minutes of IRB meetings are in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution, as required by HHS regulations at 45 CFR 46.115(a)(2). OHRP finds that, prior to January 2003, the minutes of CHOMP IRB meetings failed to include sufficient detail.

Corrective Action: OHRP acknowledges that a new template has been used to document IRB meetings that appears to include all the details required of HHS regulations at 45 CFR 46.115(a)(2). OHRP finds that this corrective action adequately addresses the allegations outlined in paragraphs (4) and (5) and is appropriate under the CHOMP assurance. OHRP recommends that the minutes include the names of the principal investigators submitting research proposals, amendments, and continuations for CHOMP IRB review.

(6) Failure of the IRB to review and approve all nonexempt human subject research covered by an assurance, in accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a). In specific, it is alleged that Dr. Rubin and/or his staff used an "IRB Stamp" to falsify IRB approval of a protocol. OHRP finds that this allegation could not be substantiated.

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,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc: Dr. Anthony Chavis, IRB Chair
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Lana Skirboll, OD, NIH
Ms. Joan Mauer, NCI, NIH

Dr. Bernard Schwetz, OHRP
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Ms. Shirley Hicks, OHRP
Ms Janice Walden, OHRP
Ms. Patricia El-Hinnawy, OHRP
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