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: 301-435-8072
FAX: 301-402-2071
E-mail:kborror@osophs.dhhs.gov

April 10, 2002

Aram V. Chobanian, M.D.
Medical Campus Provost
Boston University Medical Center
715 Albany Street
Boston, MA 02118-2526

RE: Human Research Subject Protections Under Federalwide Assurance FWA– 301

Research Project: An Evaluation of the Thalidomide Fetal Exposure Prevention Program
Principal Investigator: Allen Mitchell, M.D.
BUMC Project Number: E4403

Dear Dr. Chobanian:

The Office for Human Research Protections (OHRP) has reviewed your report of January 19, 2000 regarding the research conducted at the Boston University Medical Center (BUMC) regarding the above-reference research.

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

(1) OHRP acknowledges that FDA's approval of thalidomide was conditioned upon the implementation of the "System for Thalidomide Education and Prescribing Safety" (STEPS) program. The STEPS program requires monitoring of the safe use of thalidomide. OHRP acknowledges that the FDA has the authority to ensure and monitor the safety of an FDA-regulated product, and FDA has not approved the safe use of thalidomide outside of the STEPS program.

However, OHRP notes that the BUMC investigators and IRB considered this survey to involve human subject research, in that the investigators applied to the IRB and the IRB reviewed and

approved the study. Insofar as the survey does involve research, OHRP finds that:

(a) The procedures for enrolling subjects failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45 CFR 46.116.

(b) The informed consent documents reviewed and approved by the BUMC IRB for this research failed to include the following element required by HHS regulations at Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Required Action: Please provide OHRP with a corrective action plan to ensure that the IRB does not approve research in which procedures for enrolling subjects fail to minimize the possibility of coercion or undue influence and fails to inform subjects that participation in the research is voluntary. OHRP acknowledges that some aspects of the survey are not research, and therefore do not require review and approval by the IRB. OHRP suggests that the IRB-approved protocol be revised to indicate those activities that are not research, and those activities that are a systematic investigation designed to develop or contribute to generalizable knowledge and are therefore voluntary for subjects. OHRP recommends that BUMC work with FDA to define which data elements are necessary for STEPS and which are for voluntary research.

OHRP has the following additional concerns and questions.

(2) OHRP is concerned that the informed consent document that was used for the research may have failed to adequately address the following additional elements required by HHS regulations at 45 CFR 46.116(a)

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research (i.e., the following purposes were stated in the IRB-approved protocol but not in the informed consent document: identify the rate of pregnancy among female thalidomide users; the outcomes of pregnancies; assess the awareness of teratogenic risk, compliance with STEPS and frequency of drug sharing behavior; and, where risk of fetal exposure is high, to intervene with individual patients and prescribers);

(ii) The expected duration of the subject's participation; and

(iii) A complete description of the procedures to be followed, and identification of any procedures which are experimental. The informed consent document

did not state that if a woman considered at risk of pregnancy fails to respond to requests to follow STEPS requirements, the researchers may provide her identification number to the sponsor who could inform the pharmacy to block future prescriptions for this subject.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts (i.e., the following risks and discomforts were described in the IRB-approved protocol but not in the informed consent document: the potential discomfort of responding to questions which may be considered sensitive; and the potential for a breach of confidentiality).

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research. The IRB-approved protocol included the following possible benefits of the research that were not included in the informed consent document: increased awareness of the risks associated with thalidomide use and potential avoidance of a pregnancy which could result in an induced abortion or a malformed infant; benefits to the general public health including reduction in the burden to society caused by pregnancies resulting in malformed infants; medical scientific benefits of the experience of this system of controlled distribution and mandatory survey which will have broad implications for the regulation of other teratogenic drugs.

(d) Section 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights (should include someone other than the investigator).

Please respond. OHRP acknowledges that BUMC agreed that the IRB should, perhaps, have considered including in the informed consent document the length of time that subjects would be participating, IRB contact information, and the consequences of a subject's decision to withdraw from the research. The January 19, 2000 letter to OHRP stated that the BUMC IRB would reconsider the informed consent document. Please provide OHRP with IRB minutes of the meeting at which the informed consent document was reconsidered and any subsequently revised informed consent documents approved by the BUMC IRB.

(3) OHRP is concerned that the institution does not appear to have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) 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.

(b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, OHRP and Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. Although the policies and procedures do state that unanticipated problems and serious or continuing noncompliance need to be reported to "appropriate instititional officials," the policies do not state which officials or how this is done. The policies do not describe procedures for reporting to the IRB or OHRP.

Please respond.

OHRP offers the following additional guidance:

(4) OHRP recommends that IRBs affix the approval and expiration dates to all approved informed consent documents and stipulate that copies of these dated documents must be used in obtaining consent. This procedure helps ensure that only the current, IRB-approved informed consent documents are presented to subjects and serves as a reminder to the investigators of the need for continuing review.

Please submit to OHRP your response to the above determinations, questions and concerns no later than May 20, 2002. If upon further review of this matter you identify additional instances of non-compliance with the HHS regulations for protection of human subjects, please describe the corrective actions that have been or will be taken to address the noncompliance.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

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

cc: Dr. Jonathan Woodson, IRB Chair IRB#1, BUMC

Dr. Louis Vachon, IRB Chair IRB#2, BUMC
Dr. Richard Saitz, IRB Chair IRB#3, BUMC
Helen M. Lawless, BUMC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Michael A. Carome, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP