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
email: kborror@osophs.dhhs.gov

July 24, 2002

Keith A. Marcotte
Vice President for Research Administration
Brigham and Women's Hospital
75 Francis St.- 10BPW
Boston, MA 02115

RE: Human Research Subject Protections Under Federal Wide Assurance FWA- 484

Research Project: Molecular Genetic Epidemiologic Study on Asthma
Principal Investigator: Dr. Xiping Xu
B&WH Project Number: 94-06932

Research Project: Genetics of Airway Responsiveness and Lung Function
Principal Investigator: Dr. Xiping Xu
HHS Project Number: R01 HL56371-02
B&WH Project Number: 96-08190

Dear Mr. Marcotte:

The Office for Human Research Protections (OHRP) has reviewed your report of May 9, 2002 regarding the above-referenced research conducted by the Brigham and Women's Hospital (B&WH).

In its March 28, 2002 letter, OHRP required that B&WH develop satisfactory corrective action plans to address the following determinations made by OHRP regarding the above-mentioned research projects and B&WH's system for protecting human subjects:

A. OHRP Findings Regarding Project Number R01 HL56371-02

(1) In accordance with Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b) and 46.109(a), an Institutional Review Board (IRB) must review and approve

all non-exempt human subject research covered by an assurance. OHRP found that certain human subject research was conducted by Dr. Xu without IRB review. OHRP requested a satisfactory corrective action plan to assure that all investigators at B&WH seek IRB review and approval for all non-exempt human subject research prior to conducting that research.

Corrective Action: OHRP acknowledges that the B&WH has required that all research personnel complete a human subject research educational program, and has instituted lectures to the research community, focus groups and discussions between IRB members and investigators. A new website has been developed to provide resource documents and alerts users to changes in policies and procedures. B&WH also has developed a quality improvement program to help educate clinical investigators, improve the performance of human subject research, and ensure investigator compliance with Federal regulations, by conducting audits, site-visits, assisting investigators who are conducting self-assessments, and participating in a variety of educational activities. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH FWA.

(2) HHS regulations at 45 CFR 46.111(a)(1), (2), and (3) require respectively that, in order to approve research, the IRB shall determine that: risks to subjects are minimized; risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result; and selection of subjects is equitable. OHRP found that the IRB failed to adequately consider whether or not (a) the subjects would benefit from this research, either in the short term or the long term; (b) the risks to which they are subjected might outweigh the benefits; and (c) that the subject selection was equitable.

Corrective Action: OHRP acknowledges that since the research was initially reviewed, the B&WH IRB has undergone numerous changes and enhancements in human subject protections, including implementation of a quality improvement program, reorganization of the B&WH IRB system, implementation of new policies and procedures, and increasing the level of scrutiny to issues of risk and subject selection. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH FWA. OHRP again emphasizes that research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

(3) OHRP found that the informed consent documents reviewed and approved by the B&WH IRB for these studies failed to adequately address the following element required by HHS regulations at 45 CFR 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.

Corrective Action: OHRP acknowledges that the B&WH IRB has revised the standard clinical research consent form to include this language. OHRP finds that this corrective action

adequately addresses the above finding and is appropriate under the B&WH FWA.

(4) HHS regulations at 45 CFR 46.404-407 require specific findings by the IRB for approval of research involving children. OHRP's review of IRB documents revealed no evidence that the B&WH IRB made the required findings when reviewing this research involving children ("Molecular Genetic Epidemiologic Study on Asthma"--6 years and older; "Genetics of Airway Responsiveness and Lung Function"--8 years and older.) Although B&WH's January 30, 2002 response to OHRP stated that "[t]he importance of assent and sensitivity to the child study participant was part of standard review," this statement did not address all the required findings under HHS regulations at 45 CFR 46.404-407.

Corrective Actions: OHRP acknowledges that current B&WH IRB policies and procedures focus much more attention on the issue of child assent than previously was given. OHRP acknowledges that the B&WH IRB also has revised its human subject research initial review application form, now utilizes a special reviewer form, and circulated a memo to IRB members to ensure that the IRBs make the specific findings required by HHS regulations at 45 CFR 46.404-407 when approving research involving children. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH FWA.

(5) OHRP found that when reviewing this research, the IRB appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

Corrective Action: OHRP acknowledges that the B&WH IRB has developed numerous ways to ensure that the IRB receives and reviews sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. These include revised initial review application forms, development of guidelines for the recruitment of research subjects and advertisements for recruiting subjects, a request for detailed recruitment information on the protocol summary, review criteria consistent with 45 CFR 46.111, and revised continuing review application forms. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH FWA.

(6) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval already has been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP found that several protocol changes may have been implemented without B&WH IRB approval. In addition to requiring corrective actions, OHRP requested that B&WH consider implementing a plan to monitor any current research records on an ongoing basis to verify that Dr. Xu is conducting the research in accord with the IRB-approved protocols.

Corrective Actions: OHRP acknowledges that the B&WH has taken numerous actions to ensure that no B&WH investigator implements changes to protocols without prior IRB review and approval. These include reminding investigators of the need to obtain approval for changes in the IRB Approval Letter, in the Partner's Investigator's Responsibilities, in the required education program for research personnel, in evaluation of research at random site visits and self assessments, and at multiple education venues. In addition, Dr. Xu has been suspended from being a principal investigator on any B&WH human research project or from enrolling any subjects in a clinical study for at least three years. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH FWA.

B. OHRP Concerns Regarding Project Number R01 HL56371-02

OHRP had the following additional concerns regarding the above-referenced research project.

(7) In its March 28, 2002 letter to B&WH, OHRP expressed concern about Chinese news reports of a farmer in Toutuo, Anhui Province who was a participant in the genetic research study on asthma. The farmer told the reporter that he had blood taken from him on 2 separate occasions, November 1996 and March 1997, but neither was asked to sign nor was given an informed consent document. He stated that the researchers came later and asked him to sign a paper; he was not told what the paper said, and he could not read it without his glasses. The date on this informed consent document is apparently October of 1997. The farmer told the reporter that he did not know he was participating in the genetic study on asthma; he said he was willing to give blood so that he could get some treatment for his children's asthma.

OHRP acknowledges that B&WH cannot confirm nor deny that this subject was enrolled in the Millenium study, but he was apparently not enrolled in protocol # HL56371.

(8) In its March 28, 2002 letter to B&WH, OHRP expressed concern that several subjects in the projects "Genetics of of Airway Responsiveness and Lung Function" and "Molecular Genetic Epidemiologic Study on Asthma" may not have dated the informed consent documents themselves, or that the documents may have been back-dated.

OHRP acknowledges B&WH's statement that for these studies, the researchers dated the informed consent documents at the time of obtaining consent to ensure that the dates were all written by the Western calendar rather than the Chinese lunar year.

C. OHRP Findings Regarding General Human Subjects Protections at B&WH

(9) OHRP found that B&WH did not have adequate written IRB policies and procedures that describe many of the activities required by HHS regulations at 45 CFR 46.103(b)(4) and (5).

Corrective Action: OHRP acknowledges that the B&WH IRBs have revised their policies

and procedures to address these findings. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH FWA.

As a result, there should be no need for further involvement of OHRP in this matter with B&WH at this time. Of course, OHRP must be notified should new information be identified which might alter this determination.

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. Joseph H. Antin, Chair, IRB #1, B&WH
Dr. Julian L. Seifter, Chair, IRB #2, B&WH
Dr. Jeffrey Otten, President, B&WH
Dr. P. Pearl O'Rourke, B&WH
Ms. Laura Kea, B&WH
Dr. Xiping Xu, B&WH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Michael A. Carome, OHRP
Dr. Melody H. Lin, OHRP
Dr. Jeffrey M. Cohen, OHRP
Dr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP
Mr. Barry Bowman, OHRP