DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 17, 2001

M. David Low, M.D., Ph.D.
President
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Anne Dougherty, M.D.
IRB Chair
University of Texas - Houston
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1246

Research Project: *H. Pylori* Infection in Children on the U.S.-Mexico Border (DK-97-003)
Principal Investigator: Karen Goodman, Ph.D.

Dear Dr. Low and Dr. Dougherty:

The Office for Human Research Protections (OHRP) has reviewed your report dated August 10, 1999 regarding the University of Texas Health Science Center - Houston's (UTHSC's) response to OHRP's letter of June 18, 1999. OHRP apologizes for the delay in responding to your report.

Based upon its review of the materials submitted with your report, OHRP makes the following determinations:

(1) The membership of the UTHSC Institutional Review Board (IRB) appears to include the necessary expertise to review and approve research involving children as required by

Department of Health and Human Services (HHS) regulations at 45 CFR 46.107(a). Furthermore, OHRP acknowledges that the above referenced research was originally reviewed by a subcommittee of the UTHSC IRB which included a pediatrician.

(2) HHS regulations at 45 CFR 46.103(a) require that each institution engaged in HHS supported research involving human subjects provide a written assurance to OHRP that it will comply with the requirements set forth in the regulations for the protection of human subjects. OHRP finds that the UTHSC failed to provide the appropriate assurance to OHRP as required. Specifically, the UTHSC failed to identify the institutions at which gastric biopsies were to be performed as part of the 13C-urea validation study (i.e., Providence Memorial Hospital, Sierra Medical Center, and Columbia Hospital) and that these institutions would need to provide an assurance of compliance to OHRP.

Corrective Action: OHRP acknowledges the efforts by the UTHSC to provide Single Project Assurances to OHRP for the institutions involved in the *H. pylori* validation study. OHRP has determined this corrective action to be appropriate under the UTHSC MPA.

Please note that OHRP was not able to locate a Single Project Assurance for research conducted at the above mentioned institutions. Institutions requiring an assurance to conduct research involving human subjects must submit either an SPA or a Federalwide Assurance (FWA) to OHRP. Information on the application process for submitting an SPA or FWA can be found on OHRP's website at http://ohrp.osophs.dhhs.gov/irbasur.htm.

Please note that research supported by HHS funds involving human subjects can not proceed unless the institution has an applicable OHRP approved assurance.

(3) HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings shall be in sufficient detail to show the actions taken by the IRB and the votes on these actions. The minutes of IRB meetings supplied with your report fail to show any actions taken by the IRB relating to continuing review for the above referenced research.

Required Action: By March 30, 2001, the UTHSC must submit to OHRP a satisfactory corrective action plan to ensure that the minutes of IRB meetings meet all the requirements of HHS regulations at 45 CFR 46.115(a)(2).

At this time OHRP has the following additional questions, recommendations and guidance:

(4) HHS regulations at 45 CFR 46.116(a) require, among other things, that informed consent documents include (i) a description of the procedures to be followed; (ii) the identification of any procedure which is experimental; and (iii) a description of any reasonably foreseeable risks or discomforts to the subject.

The protocol for the *H. Pylori* Infection in Children on the US-Mexico Border Validation Study stated:

(a) "Eligible patients will be those from whom biopsies are taken during gastroscopy based on clinical judgement of Dr. Santos and whose parents sign an informed consent for participation."

(b) "Two biopsies will be sent to the Pathology Department of Louisiana State University Medical Center for histological diagnosis by Pelayo Correa, M.D., a pathologist with expertise in diagnosing *H. pylori* infection."

(c) "Two gastric biopsies taken from the antrum, at least one from the greater curvature, will be used for histological diagnosis."

Additionally, the informed consent document for use at the Providence Memorial Hospital states that two or three additional biopsy samples will be taken and that these will be sent to laboratories for analysis.

These statements suggest that the collection of biopsy samples is being directed, at least in part, by the protocol and not solely for clinical care. If so, biopsy samples collected in this fashion would be considered part of the research study and require informed consent prior to performing the procedure. The original IRB approved informed consent documents for the validation study do not indicate that any additional biopsy samples were to be taken and none of the IRB approved informed consent documents provide a description of any of the risks that might be associated with gastric biopsy. As a result, OHRP is concerned that the informed consent documents reviewed and approved by the IRB for the *H. pylori* validation study failed to include the elements required by HHS regulations at 45 CFR 46.116 (a)(1) and (2).

Please respond. With your response please indicate (i) the status of this study; (ii) whether collection of biopsy samples are dictated, in part, by the research study; (iii) at what point in the study subjects had given their informed consent; and (iv) the opinion of the UTHSC IRB as to the appropriateness of contacting the subjects if informed consent had not been properly obtained.

(5) The UTHSC guidelines for investigators indicate that should a protocol be disapproved by the IRB there exists a mechanism for appeal to the President of UTHSC, who may request an ad hoc IRB be formed for purposes of reviewing the protocol. The guidelines also indicate that such review will be made available to the IRB but may not override the decision of the IRB. The guidelines do not specify what actions might be taken after such an ad hoc IRB has reviewed the protocol.

HHS regulations at 45 CFR 46.112 stipulates that research approved by an IRB may be subject to further review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB. OHRP is concerned that the use of an ad hoc IRB would in such a situation may

violate HHS regulations at 45 CFR 46.112, as well as the UTHSC MPA, if an ad hoc panel can approve research disapproved by the IRB. Please respond.

(6) Where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

(7) The UTHSC IRB policies and procedures indicate that the subcommittee reviewing research studies receives copies of the full protocol. OHRP recommends that in conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation. All other IRB members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material. In addition, the complete documentation should be available to all members for review.

Please clarify what materials are provided to all IRB members for protocols undergoing initial and continuing review.

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,

Patrick J. McNeilly, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Dr. Palmer Beasley, Dean, UT School of Public Health
Dr. Karen Goodman, UTHSC
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg. Koski, OHRP
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