DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 3, 2001

Chi Van Dang, M.D., Ph.D.
Vice Dean for Research
The Johns Hopkins University
School of Medicine
School of Medicine Administration Building, Room 124
720 Rutland Avenue
Baltimore, MD 21205-2196

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1011

Dear Dr. Dang:

The Office for Human Research Protections (OHRP) has reviewed your first monthly progress report dated August 31, 2001, on institutional protections for human subjects at Johns Hopkins University School of Medicine (JHU SOM) and its affiliated institutions.

Based upon its review of your report, OHRP has the following comments, concerns and guidance:

(1) OHRP acknowledges that JHU SOM and its affiliated institutions have begun to implement substantive corrective actions to address the findings made by OHRP in its July 19, 2001 site visit letter and to enhance its system for protections of human subjects. OHRP acknowledges that this is a major undertaking which has required extraordinary effort by the JHU staff.

(2) OHRP would like to commend the Johns Hopkins Bayview Medical Center (JHBMC) Institutional Review Board (IRB) in particular for the quality of its reviews of research involving human subjects subsequent to the suspension of MPA M-1011 by OHRP on July 19, 2001.

(3) OHRP is concerned about the review process at convened meetings of the JHU SOM IRBs. OHRP notes that the minutes of meetings of the SOM IRBs suggest that for many protocols, the IRB chair dominates the discussion. This process appears to dampen substantive discussion of important issues by IRB members. Please respond.

(4) OHRP is concerned that on occasion when reviewing research, the IRBs failed to obtain sufficient information necessary to make all determinations required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.111 prior to approving the research. For example, OHRP notes the following:

> (a) Protocol # 97-02-19-03, reviewed and approved on July 24, 2001 by one of the SOM IRBs. The discussion includes a statement from the principal investigator that "you don't have the whole protocol." Furthermore, one member expressed concerns about the adequacy of the informed consent document and stated "I think [the informed consent document is] inaccurate in the way I read it, but it's not worth holding up the study to fix it. We should fix it later."
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> (b) Protocol # 01-03-13-05, reviewed and approved on July 24, 2001 by one of the SOM IRBs. During the discussion, one IRB member asked the principal investigator to explain how dose escalation of the investigational agent being tested was to be done. The investigator replied that "[p]resumably…it's in the full protocol, which I don't have with me right now."
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> (c) The minutes of several IRB meetings described instances where protocols were closed to enrollment and the primary reviewers indicated that it was not necessary to review the informed consent document. OHRP notes that the adequacy of informed consent is paramount in providing proper protection for human subjects. For such protocols where (a) the informed consent documents may have been deficient; and (b) already enrolled subjects were still undergoing research interventions or interactions, it would be appropriate for the IRB to review the informed consent documents and determine whether already enrolled subjects should be provided with additional information which was not provided when the subjects first enrolled.

Please respond.

(5) OHRP is concerned that for some research protocols documents were not distributed to IRB members prior to convened meetings. For example, OHRP notes the following:

> (a) Protocol # 01-04-30-01, reviewed and approved on July 23, 2001 by one of the SOM IRBs. It appears that the IRB permitted an investigator, who was not a member of the IRB, to add this protocol to the end of its agenda without any IRB member receiving or reviewing relevant protocol documents prior to the meeting. Furthermore, the investigator appears to have been the only individual who reviewed protocol documents and he performed the function of primary reviewer. Nevertheless, the IRB approved the protocol.
>
> (b) Protocol # HBV96-11-25-02, reviewed by the JHBMC IRB on August 6, 2001. The discussion suggests that relevant documents necessary for review of the protocol were not distributed to IRB members prior to the review.

> (c) Protocol # ARC92-08-12-02, reviewed by the JHBMC IRB on August 6, 2001. At this meeting the primary reviewer stated "there seems to be an updated protocol...but I haven't had a chance to read it yet." This statement appears to imply that the primary reviewer was not prepared for the meeting.

Please respond.

(6) HHS regulations at 45 CFR 46.408(a) require that the IRB determine, as necessary, that each protocol involving children as subjects makes adequate provisions for soliciting the assent of the children. OHRP notes that for research not eligible for expedited review, the convened IRB is responsible for making this determination. OHRP is concerned that, on occasion, the JHU IRBs failed to determine whether assent was needed and to ensure, as necessary, that researchers made adequate provisions for soliciting the assent of children subjects. For example OHRP notes the following:

> Protocol # 93-12-27-02, reviewed and approved by one of the SOM IRBs on July 21, 2001. The minutes of the IRB meeting appear to indicate that the IRB, despite having insufficient information regarding the provisions for soliciting the assent of children, approved the protocol and deferred resolution of this matter to a subcommittee.

Please respond.

(7) HHS regulations at 45 CFR 46.111(a)(3) require that in order to approve research the IRB must determine that the selection of subjects is equitable and should be particularly cognizant of the special problems of research involving vulnerable populations. HHS regulations at 45 CFR 46.111(b) require that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included to protect that rights and welfare of these subjects.

IRBs should look closely at the potential vulnerability of the subject population for all research protocols. Vulnerable populations are not limited to those groups identified in 45 CFR Part 46, Subparts B, C, and D.

OHRP is concerned that the JHU IRBs failed to ensure that the above requirements were satisfied for some to research involving vulnerable populations. Although the JHU IRBs appear to be making appropriate determinations for research involving children, it appears that when reviewing other protocols, the IRBs failed to recognize and consider other populations which were likely to be vulnerable. For example, OHRP notes the following:

> Protocol # 98-05-21-05 (PET Assays of Striatal Dopamine Markers in Cocaine Craving), reviewed and approved by one of the SOM IRBs on August 8, 2001. The chair stated that consideration of vulnerable populations was not applicable

with respect to the informed consent document for this protocol. In addition, this protocol offers a payment of $600-700 for 2-4 days involvement in the study, for which the IRB had little comment. OHRP is concerned that the IRB failed to recognize the vulnerability of drug abusing populations and the possibility of coercion or undue influence to participate by offering a large payment.

Please respond.

(8) OHRP understands that the JHU IRBs are reviewing informed consent documents in conjunction with a checklist to ensure that the required elements for informed consent stipulated by HHS regulations at 45 CFR 46.116 are included. OHRP is concerned that for certain protocols the IRBs have not adequately reviewed the elements of the informed consent document. For example, OHRP notes the following:

Protocol # 99-08-11-01, reviewed by one of the SOM IRBs on August 6, 2001. The IRB identified issues related to the disclosure of alternatives to participation in the research. Specifically, when asked if additional alternatives should be added to the informed consent document, one IRB member indicated that the informed consent document had a statement that if other alternatives are available they will be discussed with the subject and that should be sufficient.

HHS regulations at 45 CFR 46.116(a)(4) states that in seeking informed consent, each subject should be provided with a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject must be included. OHRP is concerned that the IRB made no changes to the informed consent document prior to approving the research.

Please respond.

(9) HHS regulations at 45 CFR 46.107(a) stipulate that an IRB shall be sufficiently qualified through the experience and expertise of its members to promote respect for its advice and counsel, and must possess the professional competence necessary to review specific research activities. OHRP is concerned that the SOM IRBs on occasion have reviewed and approved research without having members with sufficient background and expertise in fields relevant to the research. For example, OHRP notes the following:

(a) At its July 23, 2001 meeting, the IRB reviewed and approved oncology clinical trials without a member with oncology experience and background being present. Indeed, the Chair at one point stated “I wish we had an oncologist here,” and another member stated “I think we need an oncologist.”

(b) At its July 31, 2001 meeting, the IRB approved a clinical trial that was to be conducted in Brazil. It is unclear which members of the IRB had expertise regarding the local context where this research was to be conducted.

Please respond.

(10) HHS regulations at 45 CFR 46.111(a)(1) require that the IRB shall determine that the risks to the subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk. OHRP has concerns that the JHU SOM IRBs may not be adequately reviewing certain protocols with respect to the scientific soundness of the research. OHRP notes that there are many instances in the minutes of IRB meetings where the chair referred to scientific review of protocols by other bodies (e.g., the National Institutes of Health) and stated that the design therefore is sound. OHRP is concerned about such assumptions given the IRB's responsibility to make this determination under 45 CFR 46.111(a)(1). Please respond.

(11) HHS regulations at 45 CFR 46.111(a)(2) require that an IRB shall determine that the risks to subjects are reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result. Based upon the discussion of some clinical trials, OHRP is concerned that the SOM IRBs fail to appreciate and consider the difference in probability of benefit between phase I, II, and III clinical trials. For example, OHRP notes the following:

(a) Protocol # 00-02-08-04, A Phase I/II Study of Extended Field Radiation Therapy with Concomitant Paclitaxel and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to the Para-Aortic Lymph Nodes. The minutes of the July 21, 2001 IRB meeting include the following statement by the Chair:

> "Even though this is a Phase I study, the hope is there can be some disease control."

(b) Protocol # 00-02-24-03, Phase II Evaluation of Oxaliplaten in the Treatment of Persistent Endometrial Carcinoma. The minutes of the July 21, 2001 IRB meeting include the following statement by the Chair:

> "…there is, however, the prospect of direct benefit given that the hope is that there would be control of disease."

(c) Protocol # 01-03-13-05, Phase I Study of Gadolinium-Texaphyrin and Involved Field Radiation Therapy for Intrinsic Pontine Glioma in Children. The minutes of the IRB meeting on July 24, 2001, include the following statement by the Chair:

> "I reason that there was a chance that an individual might benefit."

Please respond.

(12) HHS regulations at 45 CFR 46.116 require that investigators seek legally effective informed consent from subjects or their legally authorized representatives only under circumstances that minimize the possibility of coercion or undue influence. OHRP is

concerned that the Chairs of the SOM IRBs consider the provision of medical care at no cost under a research protocol to be a direct benefit of the research and fail to recognize that such free care could result in an undue influence on subjects (for example, see discussion of protocol # 92-05-01-02 at the July 21, 2001 IRB meeting; discussion of protocol # 01-04-30-01 at the July 23, 2001 IRB meeting; and discussion of protocol # 99-02-05-03 at the July 31, 2001 meeting). Please respond.

(13) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings document the vote on all actions, including the number voting for, against, and abstaining. OHRP found that the minutes of some IRB meetings failed to satisfy this requirement (e.g., see minutes of IRB meetings on July 23, 24, 25, 26, and 27, 2001). Please note that recording votes as "unanimous" is not sufficient. Please respond.

(14) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP is concerned that on occasion the SOM IRBs may have failed to satisfy this requirement. For example, regarding the July 25, 2001 meeting of one of the SOM IRBs, OHRP notes that (a) Dr. Cindy Schwartz is listed in the minutes as a member being present; (b) Dr. Schwartz was an investigator on several protocols reviewed and approved by the IRB; and (c) votes on these actions are recorded as unanimous with no indication as whether Dr. Schwartz abstained. Please respond.

(15) OHRP is concerned that certain protocols approved by the IRBs by expedited review may not have been eligible for an expedited review procedure. OHRP understands that some protocols may have already been closed to enrollment and may have satisfied the requirements for expedited review; nonetheless, OHRP is unclear about the status of certain studies. A list of protocols for which OHRP has particular concern is attached (Tab 1). Please respond.

(16) Regarding your request to permit the Pharmacy and Therapeutics (P&T) Committee to delegate to its members on the IRBs the authority to approve protocols that involve the use of drugs, please note that HHS regulations at 45 CFR Part 46 do have provisions that are pertinent to an institution's P&T Committee. Should the JHU P&T committee wish to delegate its authority to a member of the IRB, OHRP has no objection to such an arrangement. OHRP wishes to point out that HHS regulations at 45 CFR 46.107(a) require that in addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitment and regulations, applicable law, and standards of professional conduct and practice.

(17) Regarding your request to amend your July 21, 2001 corrective action plan to allow authority for approval of minor changes in protocols to be delegated to an IRB member, OHRP does not object to this change. HHS regulations at 45 CFR 46.110(b)(2) allow for expedited review of minor changes in previously approved research during the period for which approval is authorized. Furthermore, this regulation stipulates that the expedited review may be carried out by the IRB chairperson or by one or more experienced

reviewers designated by the chairperson from among the members of the IRB.

(18) OHRP would like to remind JHU that HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings shall be in sufficient detail to show (i) attendance at te meetings; (ii) actions taken by the IRB; (iii) the vote on these actions including the number of members voting for, against and abstaining; (iv) the basis for requiring changes in or disapproving research; and (v) a written summary of controverted issues and their resolution. OHRP notes that, in general, the minutes of IRB meetings provided with your August 31, 2001 progress report appear to meet the requirements of 45 CFR 46.115(a)(2). JHU may wish to consider alternatives to collecting verbatim transcripts for use as minutes of IRB meetings.

OHRP has also reviewed your August 24, 2001 report regarding RPN 82-02-24-01, entitled "Studies of Hormone Action in Patients with Altered G-Protein Coupled Signal Transduction" (Principal Investigator - Dr. Michael A. Levine). Based upon its review, OHRP makes the following determinations:

(19) OHRP finds that the informed consent documents reviewed and approved by the SOM IRB and used to enroll subjects prior to July 2001 failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): a description of the procedures to be followed, and identification of any procedures which are experimental. In particular, the informed consent document failed to describe the following procedures: thyrotropin stimulation test, glucagon stimulation test, cortrosyn stimulation test, gonadotropin releasing hormone (GnRH) stimulation test, L-arginine and growth hormone releasing hormone stimulation tests with and without L-dopa administration, and brain MRIs.

(b) Section 46.116(a)(2): a description of the reasonably foreseeable risks and discomforts. For example, the informed consent document listed the side effects of administered medications as "...feeling sick to your stomach, dizzy or slightly warm." However, the informed consent document failed to describe (i) the other risks of administration of drugs such as L-dopa and GnRH such as cardiac irregularities and hypotensive or bradykinetc episodes (for L-dopa), and anaphylaxis or other hypersensitivity reactions (for GnRH); (ii) risks of MRI including claustrophobia or anxiety attacks; and (iii) the risk of thrombophlebitis secondary to indwelling intravenous catheters.

(c) Section 46.116(a)(4): A description of appropriate alternative procedures or courses of treatment that might be advantageous to the subject.

(d) Section 46.116(a)(7): An explanation of whom to contact for answers to questions about research subjects' rights.

(e) 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.

OHRP has the following additional concerns and questions regarding RPN 82-02-24-01 and your August 24, 2001 report:

(20) It appears that the revisions to the informed consent document provided with your August 24 report were not made until after OHRP raised concerns about the adequacy of the informed consent document in its August 10, 2001 letter.

OHRP notes that this protocol was reviewed and approved by one of the SOM IRBs on July 30 and 31, 2001. OHRP is concerned that although the IRB reviewed the informed consent document for this protocol at its July 30 and 31, 2001 meetings, it failed to require any revisions to the informed consent document.

OHRP believes that the issues it raised in its August 10, 2001 letter, particularly the issues related to the description of the procedures involved in the research, are among the most fundamental with respect to the review of research. OHRP is concerned about the failure of the SOM IRB to identify these deficiencies in the informed consent document.

Please respond.

(21) Based on review of the materials submitted with your August 24, 2001 report, it appears that it may have been appropriate for the informed consent document to include the following additional elements in accordance with HHS regulations at 45 CFR 46.116(b):

(a) Section 46.116(b)(2): Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(b) Section 46.116(b)(4): The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(c) Section 46.116(b)(5): A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

Please respond.

(22) HHS regulations at 45 CFR 46.116 require that the information provided in the informed consent documents be in language understandable to the subject. OHRP is concerned that the language in the revised informed consent document provided with your August 24, 2001 report appears to be overly complex, particularly where it makes reference to hormone signals, gene defects and hormone responsiveness. Please respond.

(23) HHS regulations at 45 CFR 46.116 require that informed consent must be obtained under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. OHRP is concerned that the procedures for recruitment of subjects into the study and encouraging them to remain in the study may have failed to minimize the possibility of coercion or undue influence. In particular, OHRP notes the following:

(a) The Alternatives to Participation portion of the informed consent document states, "You may decide to have these same tests as routine tests but then you will be responsible for the costs."

(b) The copy of the recruitment letter addressed to families of potential subjects discusses free growth hormone until 2002 and the revised informed consent document provided with your report states, "...in some cases, we may be able to provide medication at no cost." However, your August 24, 2001 report stated, "Subjects are informed of this benefit only if they meet all of the Genentech Center requirements."

Please respond. In your response, please explain the apparent discrepancy between statements made in the recruitment letter and your August 24, 2001 report.

(24) OHRP is concerned that the JHU IRB failed to determine that the above-referenced research satisfied the criteria for approval of research involving children under HHS regulations at 45 CFR 46.404-407. In specific, OHRP is concerned that the above-referenced research appears to be more than a minor increase over minimal risk and provide no direct benefit to the subject and therefore is not approvable under HHS regulations at 45 CFR 46.404-406. Please respond.

(24) This protocol appears to involve normal subjects. OHRP is concerned that the records provided with your report did not include a separate informed consent document to be used for such subjects. Please respond.

OHRP Action

After reviewing your reports and as discussed in our September 13, 2001 telephone conversation and e-mails, OHRP has determined that progress reports regarding implementation of JHU SOM's corrective action plan and education programs for all IRB members, all IRB staff, and all investigators may be submitted on a quarterly basis. This action does not otherwise alter the previously imposed restrictions on the JHU MPA (M-1011) by OHRP.

The next progress report, due no later than November 30, 2001 should include the following:

(1) A status report on the implementation of each proposed corrective action.

(2) A detailed response to the above findings, concerns, and questions.

(3) A summary of the progress made in implementing the planned educational programs

for all IRB members, all IRB staff, and all research investigators about the ethical principles and regulatory requirements for the protection of human subjects. Please include a summary of educational activities completed by IRB members and staff since July 19, 2001, as well as expected educational opportunities to be provided over the next 12 months.

(4) A summary of the IRBs' progress in reviewing all suspended research projects.

(5) For each IRB, copies of minutes for three meetings between September and November 2001.

(6) A copy of any revised written IRB policies and procedures.

(7) A detailed description of the duties and responsibilities of each IRB staff member. For each staff member, please include the percentage of time dedicated to IRB functions versus other non-IRB functions.

(8) If any independent or commercial IRB is designated under the JHU SOM MPA, a description of the procedures that have been or will be implemented to ensure that such IRB has an adequate knowledge of the local research context for JHU SOM and all of its affiliated institutions.

Please note that OHRP anticipates conducting an on-site review of IRB records at the JHU SOM and JHBMC after the submission of the November 30, 2001 quarterly progress report.

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

Enclosure: Expedited review list

cc: Mr. Ronald R. Peterson, President, The Johns Hopkins Hospital
Dr. Sue K. Donaldson, Dean, School of Nursing, JHU
Dr. Jacquelyn Campbell, School of Nursing, JHU
Dr. Gary Goldstein, President, Kennedy Krieger Institute
Ms. Karen Cox, Research Administrator, Kennedy Krieger Institute
Dr. Darrell R. Abernethy, Clinical Director, NIA
Mr. Richard P. Suess, Chief of Staff, Applied Physics Laboratory
Mr. David Grant, Applied Physics Laboratory

Ms. Barbara L. Starklauf, Administrator, Human Subjects Committees, JHU SOM
Dr. Lewis Becker, Chairman, JCCI -I, JHUSOM
Dr. David R. Cornblath, Chairman, JCCI-II, JHU SOM
Dr. Paul Lietman, Chairman, JCCI-III, JHU SOM
Dr. Paul Braine, Chairman, JCCI-IV, JHU SOM
Dr. Gary Briefel, Chairman, JHBMC-1 IRB
Dr. Judith Stiff, Chairman, JHBMC-2 IRB
Commissioner, FDA
Dr. David Lepay, FDA
Dr. James F. McCormack, FDA
Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Ms Roslyn Edson, OHRP