DEPARTMENT OF HEALTH & HUMAN SERVICE

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: 240-453-8132
FAX: 240-453-6909
Email: Kristina.borror@hhs.gov

June 23, 2008

Murray G. Ramsden, HBA, DHA, CHE
Chief Executive Officer
Interior Health Authority
Kelowna, British Columbia V1Y 4N7
CANADA

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 10352

Dear Dr. Ramsden:

Thank you for your January 30, February 29, and May 14, 2008 reports responding to our December 18, 2007 letter regarding compliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

A. Determinations

In our December 18, 2007 letter, we made the following determinations:

> (1) We determined that the Interior Health Authority (IHA) did not have written institutional review board (IRB) procedures that adequately described 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 continuing review of research.
> >
> > (b) The procedures which the IRB will follow for reporting its findings and actions to the institution.
> >
> > (c) 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.
> >
> > (d) 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.

(e) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and the Office for Human Research Protections (OHRP) of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Corrective Action: We acknowledge that IHA has developed written IRB procedures to address these activities, except the procedures for ensuring prompt reporting to any department or agency head and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

Required Action: By August 4, 2008 please provide us with a copy of the written procedures that address the regulatory requirements for reporting to department or agency heads and OHRP.

(2) HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. In our May 24, 2007 letter we expressed a concern that the IRB written procedures for the IHA IRB stated "A quorum will be the Chair...and not less than four of the standing members or substitute members…." As the IHA IRB has 11 members, this would not be a majority of members and therefore would not constitute a quorum under HHS regulations; in addition, this procedure did not include a statement regarding the regulatory requirement for including at least one member whose primary concerns are in a nonscientific area.

Corrective Action: We acknowledge that the IHA Terms of Reference for the IHA IRB have been revised to address quorum requirements. We determine that this corrective action adequately addresses our concern and is appropriate under the IHA FWA.

(3) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be 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. We determined that IHA and Penticton IRB minutes failed to meet some of these requirements. In specific, the minutes did not include the vote on 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.

Corrective Action: OHRP acknowledges that in the revised Terms of Reference, the requirement for recording of voting, the basis for requiring changes in or disapproving research;

and a written summary of the discussion of controverted issues has been made explicit. However, the meeting minutes provided to us for IRB meetings held on February 7 and March 6, 2008 still do not include the votes on most actions taken by the IRB, but merely indicate "approval was by consensus."

Required Action: By August 4, 2008 please provide us with a corrective action to ensure that minutes of IRB meetings include documentation of the votes on all actions including the number of members voting for, against, and abstaining.

We make the following additional determination:

(4) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. We determine that the IHA IRB failed to conduct continuing review of research at least once per year for the protocol "Albumin in Acute Stroke: ALIAS." We note that the study was initially approved November 6, 2006 and was not reviewed and approved again until February 7, 2008.

Required Action: By August 4, 2008 please provide us with a corrective action to address this finding.

B. Guidance

We offer the following guidance:

(1) We recommend that you include more operational details in your IRB procedures for:

(a) the procedures which the IRB will follow for conducting its continuing review of research, particularly for review at convened meetings; and

(b) 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.

(2) We recommend that the Standard Operating Procedure: REB B0200 - CONTINUING ETHICS REVIEW: AMENDMENTS – CLINICAL TRIALS, broaden the definition of amendments to any changes in research activities.

(3) We recommend that the Standard Operating Procedure: REB B0300 - CONTINUING ETHICS REVIEW: ANNUAL STATUS REPORT AND RENEWAL – CLINICAL TRIALS, under the section title "Review Phase" be modified to more accurately describe the circumstances under which research is eligible for continuing review in an expedited manner, e.g., research that involves not greater than minimal risk **and** appears on the specific research categories published in the Federal Register at 63 FR 60364—60367, and for continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; **and** (ii) all subjects have completed all research-related interventions; **and** (iii) the research remains active only for long-term follow-up of subjects; **or**

(b) where no subjects have been enrolled and no additional risks have been identified; **or**

(c) where the remaining research activities are limited to data analysis.

We appreciate the continued commitment of your institution to the protection of human research subjects. Please feel free to contact me should you have any questions.

Sincerely,

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

cc: Dr. Anne-Marie Broemeling, Director, Research & Evaluation, Strategic Information & Planning, IHA
Ms. Susan Valley, Chairperson, Penticton Regional Hospital IRB
Ms. Beryl A, Ferguson, Chairperson, IHA IRB
Commissioner, FDA
Dr. Joanne Less, FDA
Ms. Lou Valdez, OGHA
Dr. Sherry Mills, NIH
Dr. Joe Ellis, NIH