DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

FEB 5 2009

By Certified Mail – Return Receipt Requested
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CBER – 09 – 03

Warning Letter

Gary B. Weinstein
Executive Vice President and IRC Chair
The Washington Hospital IRC
155 Wilson Avenue
Washington, Pennsylvania 15301-3336

Dear Mr. Weinstein:

This letter describes the results of a Food and Drug Administration (FDA) inspection of The Washington Hospital Institutional Review Committee (IRC) that concluded on October 7, 2008. The FDA investigator conducted an inspection of the IRC to determine whether the IRC's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to review IRC operations.

At the end of the inspection, the FDA investigator issued and discussed with you the Form FDA 483, Inspectional Observations. From our review of the establishment inspection report, the exhibits submitted with the report, and the Form FDA 483, we have determined that the IRC significantly violated applicable federal regulations governing the operation and responsibilities of Institutional Review Boards (IRBs) as published under 21 CFR Parts 50 and 56 (available at http://www.gpoaccess.gov/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below. We are addressing this letter to you under 21 CFR 56.120(a) as the current IRC Chairperson with responsibility for ensuring that the IRC takes the actions necessary to bring the IRC into full compliance with FDA regulations. Under 21 CFR 56.120(a) we are also sending copies of this letter to the responsible head of the IRC's parent institution, The Washington Hospital, because under 21 CFR 56.120(c), the parent institution is presumed to be responsible for the IRC's operations.

1. **Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present. [21 CFR § 56.108(c)].**

   A. Mail ballot voting was used for all of the following approvals including the final approval to a study involving an exception from informed consent

requirements for emergency research under 21 CFR 50.24. Except for expedited review of certain kinds of research involving no more than minimal risk, or minor changes in research, review of proposed research must be conducted at a convened meeting at which a majority of the membership of the IRB is present, including one member whose primary concerns are non-scientific. The use of a mail ballot to vote on issues before the IRB is not permitted because this method does not constitute a convened meeting.

Study	Date of IRC Approval by Mail Ballot
[redacted]	4/27/05 - approved for an additional year (5/4/05 through 5/3/06)
[redacted]	11/04 - approved for an additional year through12-2-05
[redacted]	11/04 - approved for an additional year through 12-2-05
[redacted]	11/30/04 - initial approval
[redacted]	1/19/05 - approved extension
[redacted]	10/9/06 - approved through 10/8/07

B. According to the minutes of meetings convened 3/13/06 and 8/9/00, the IRC approved research on new protocols and reviewed consent forms without the majority of IRC members in attendance. The current IRC roster, last revised 3/8/04, lists nine members, but only four voting members were in attendance at the 3/13/06 meeting. Previous IRC rosters were not retained, but the 8/9/00 meeting minutes include after each IRC action, "proxies for approval were received" from four individuals. Since four other members were present at the 8/9/00 meeting, it can be concluded that there were at least eight members on the roster in 2000 and therefore a majority was not present at this meeting.

2. Failure to prepare, maintain, and follow adequate written procedures designed to assure the protection of the rights and welfare of human subjects.
[21 CFR §§ 56.102(g), 56.108(a) and (b), 56.109(b), (c), and (d), and 56.115].

A. According to *ARTICLE VI – MEETINGS* in the IRC's written procedures, contained in a document titled "INSTITUTIONAL REVIEW COMMITTEE

BY-LAWS AND PHILOSOPHY," normal meetings will be held annually or as may be required at the call of the Chair, but not less frequently than annually. However, the IRC meeting minutes illustrate that this committee reviews research at convened meetings on a sometimes infrequent basis. As shown in the table below, convened meetings held from 2002 to 2008 did not always meet this requirement.

Year	Date(s) of convened meetings
2002	3/28/02, 7/2/02, 11/14/02
2003	No convened meetings
2004	No convened meetings
2005	12/16/05
2006	3/13/06, 5/9/06, 6/23/06
2007	3/13/07
2008	6/3/08

B. According to *ARTICLE VI – MEETINGS* in the written procedures, the IRB will review each study periodically at intervals appropriate to the degree of risk but not to exceed one year. As shown below, continuing reviews were not always conducted within one year or less. Furthermore, the IRB granted approval periods that exceeded one year. The IRC often reviewed ongoing research several months before the expiration date or after the expiration date, yet the study was given an additional year approval from the previous expiration date, rather than the date it was actually reviewed. This resulted in an expiration date of greater than twelve months from the date of the IRC review and/or a lapse in approval. This practice occurred in at least 9 of 13 studies described in *The Washington Hospital IRC Committee Update* report dated 9/17/08. One medical device study example is shown in the following table.

Date	Action	Approval period
5/4/01	Initial approval	undesignated
3/28/02	Approved for an additional year	5/4/02 – 5/3/03
4/21/03	Approved for an additional year	5/4/03 – 5/3/04
6/9/04	Approved for an additional year	5/4/04 – 5/3/05
4/27/05	Approved for an additional year	5/4/05 – 5/3/06
5/9/06	Approved for an additional year	5/4/06 – 5/3/07
3/9/07	Approved for an additional year	5/4/07 – 5/3/08
6/3/08	Approved for an additional year	5/4/08 – 5/3/09

C. The Washington Hospital IRC's written procedures are not adequate for a number of reasons, including but not limited to the following:

i. There are no written procedures for the following activities:
- Review of research involving an exception from informed consent requirements for emergency research to ensure that the IRB has found and documented that specific criteria have

been met and to ensure that additional protections of the rights and welfare of the subjects will be provided.
- How the IRC conducts its continuing review of research.
- How the IRC determines which projects require review more often than annually.
- How the IRC ensures that changes in approved research, during the periods for which IRC approval had already been given, are not initiated without IRC review and approval (except where necessary to eliminate apparent immediate hazards to subjects).
- How the IRC ensures prompt reporting to appropriate institutional officials and FDA of any instance of serious or continuing noncompliance.
- Review of research involving vulnerable populations such as pregnant women, prisoners, and minors.

ii. The following written procedures do not comply with the requirements of 21 CFR Part 56:
- *Article V – Quorum* defines quorum as a majority of the committee members or four (4), whichever is less. 21 CFR 56.108(b) requires that a majority of members be present at convened meetings.
- *Article VIII – Expedited Review* states all studies submitted to the IRC shall be reviewed by the full committee, except for certain studies involving no more than minimal risk, for minor changes in research previously approved by the IRC, and for renewals of studies previously approved by the IRC. 21 CFR 56.110 does not allow for the expedited renewal of previously approved studies, but may be used for minor changes in previously approved research during the period of 1 year or less for which approval is authorized.
- *Article X – Records, Item C* defines a retention period of two years following the date of study completion. However, 21CFR 56.115(b) requires that records be retained for at least 3 years after completion of the research.
- The IRC procedures cite the Federal Register dated Friday, November 11th, 1977, Part III as a reference for at least three of its procedures. This is an inappropriate reference because this is a Food and Drug Administration Final rule for the Investigational Device Exemption Requirements for Intraocular Lenses, 21 CFR Part 813, which has since been rescinded.

iii. The IRC's written procedures for review of informed consent documents do not refer to all provisions required by 21 CFR Part 50. For example, the procedures do not explain that informed consent documents must include a statement that the study involves research, an explanation of the purposes of the research

and the expected duration of the subject's participation, and identification of any procedures which are experimental.

3. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR §§ 56.115(a)(2) and 50.24].

A. The IRC meeting minutes have not been prepared in sufficient detail to show the number of members voting for, against, and abstaining for the actions taken.

B. The 5/9/06 meeting minutes indicate the IRC approved the [redacted] study to proceed with community consultation and public disclosure with community groups. The IRC records fail to document in sufficient detail whether the IRC made specific determinations as required by 21 CFR 50.24. Also, the IRC gave the final approval on 10/9/06 for the [redacted] project after community consultation and public disclosure, but did so by mail ballot so there are no meeting minutes, as referenced in item 1A, above.

4. Failure to fulfill requirements for expedited review. [21 CFR § 56.110(b)(1)].

An IRB may review certain research using an expedited review procedure if the research involves no more than minimal risk to subjects and/or there were minor changes in previously approved research during the period for which approval is authorized. The IRC Chair inappropriately used the expedited review process for continuing review of research. Although there were no convened meetings between 11/14/02 and 12/16/05, the following table shows research approved under the expedited review procedure during this period.

Study	Date	Action
[redacted]	5/4/01 4/21/03 6/9/04 4/27/05	Approved by IRC Approved for an additional year Approved for an additional year Approved for an additional year
[redacted]	7/2/02 10/14/03 6/29/04 1/19/05	Approved by IRC Approved a one year extension Approved an additional year Continued access approved by IRC
[redacted]	11/14/02 11/26/03	Approved by IRC Approval will continue until the anticipated end of the study (7/1/05)
[redacted]	7/8/03 11/1/04 10/26/05	Approved by IRC Extension approved through 10/31/05 Extension approved through 10/31/06

5. Failure to meet the requirements for review of research involving an exception from informed consent for emergency research. [21 CFR §§ 56.109(c) and 50.24].

Under 21 CFR 56.109, an IRB must review, and has authority to approve, require modifications in, or disapprove a proposed clinical investigation. For emergency research being conducted under 21 CFR 50.24, the IRB must also evaluate materials to determine whether the investigation satisfies the criteria in 21 CFR 50.24(a) and find and document whether it is appropriate to proceed under this section. Specifically, IRBs are expected to review plans for community consultation and public disclosure and must find and document that both of these will be provided prior to the start of the study. The Washington Hospital IRC approved the [redacted] study on 10/9/06 and failed to document that the study met the criteria set out in 21 CFR 50.24. Additionally, although the clinical investigator states that he conducted the community consultation and public disclosure activities, there is no documentation that the IRC evaluated these materials and determined that these additional protections would be provided prior to start of the study as required by 21 CFR 50.24.

This letter is not intended to contain an all-inclusive list of deficiencies in the operations of the IRB.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures and recent meeting minutes with your response. Also, for any plans of action, please include the projected completion dates for each action to be accomplished.

Your failure to adequately respond to this letter and take appropriate corrective action may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions could include FDA withholding approval of new studies reviewed by your IRB that are subject to Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to 21 CFR Parts 50 and 56, terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Janet White
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1488
Telephone: (301) 827-6336

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: Thomas D. Gardine, District Director
Food and Drug Administration
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