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Inspections, Compliance, Enforcement, and Criminal Investigations

Columbia University Medical Center RDRC 9/20/11



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 11-HFD-45-09-0

G. Michael Purdy, Ph.D.
Executive Vice President for Research
Columbia University in the City of New York
535 West 116th Street
313 Low Library, Mail Code 4310
New York, NY 10027

Dear Dr. Purdy:

Between May 9, 2011, and May 17, 2011, Mr. Richard Fejka, Mr. Thomas Hansen, and Mr. Robert Steyert, representing the U.S. Food and Drug Administration (FDA), inspected the Radioactive Drug Research Committee (RDRC) at Columbia University Medical Center (CUMC). The purpose of this inspection was to determine whether the RDRC is in compliance with Title 21 of the Code of Federal Regulations (CFR), part 361. These regulations apply to radioactive drugs for human research that are generally recognized as safe and effective when administered under the conditions specified in the RDRC regulation (21 CFR 361.1). We are aware that at the conclusion of the inspection, our investigators presented and discussed Form FDA 483, Inspectional Observations, with Dr. David J. Brenner (RDRC's Chairman) and other University officials.

From our review of the establishment inspection report, the documents submitted with the report, and the Columbia University Medical Center's June 6, 2011, written response to the inspection findings, we conclude that the RDRC failed to adhere to the applicable statutory requirements and FDA regulations governing the use of radioactive drugs for human research. We note that on April 7, 2010, FDA's Center for Drug Evaluation and Research (CDER) informed Columbia University Medical Center that all Investigational New Drugs (INDs) using PET radioactive drugs manufactured at Kreitchmar PET Center (KPC) for research, were to be placed on clinical hold. The clinical hold included all RDRC-approved studies that employed the use of a PET radioactive drug produced by KPC.

Based on the results of the FDA inspection, we wish to emphasize the following:

The RDRC failed to assure the necessary conditions so that radioactive drugs used in research under their purview are considered safe and effective [21 CFR 361.1(b)(1)]. Specifically;

1. The RDRC failed to assure the quality of radioactive drugs [21 CFR 361.1(d)(6)].

An RDRC shall assure that all radioactive drugs used in the research studies "meet appropriate chemical, pharmaceutical,

radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed for safety, and be of such uniform and reproducible quality as to give significance to the research study conducted." In addition, the RDRC "shall determine that radioactive materials for parenteral use are prepared in sterile and pyrogen-free form." Our inspection revealed that the RDRC failed to assure the quality of radioactive drugs.

Specifically, no records were provided during the FDA inspection to document that any of the radioactive drugs studied under the purview of the RDRC met appropriate radionuclidic standards of identity and purity as needed for safety. In addition, there is no documentation to indicate that the RDRC assured that radioactive drugs for parenteral use are prepared in sterile and pyrogen-free form.

2. The RDRC failed to assure that investigators immediately report all adverse events (effects) associated with the use of the radioactive drug in the research study [21 CFR 361.1(d)(8)].

An RDRC shall assure that investigators immediately report to the RDRC all adverse effects associated with the use of the radioactive drug in the research study. The regulations also state that all adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the RDRC to the FDA. Our inspection revealed that adverse effects did occur in research that should have been reported to the RDRC; however, these adverse events were not reported to the RDRC for review.

In particular, FDA investigators reviewed case report forms for Subjects **(b)(6)**, **(b)(6)**, and **(b)(6)** enrolled in Studies **#(b)(4)**, **#(b)(4)**, and **#(b)(4)** respectively, and found documentation of several adverse experiences. For example, case report forms revealed headache, dizziness, and sore throat among those subjects. However, these adverse effects were not reported to the RDRC for review.

During the inspection, Dr. Brenner acknowledged that no adverse events had been reported to the RDRC since he became Chairman in January 2007, and that there is no mechanism in place for the RDRC to receive such reports which would allow the RDRC to determine the need to report events attributable to the radioactive drug to the FDA.

3. The RDRC failed to review and approve research at meetings at which a quorum, defined as more than 50% of the membership (including appropriate representation from the required fields of specialization), is present [21 CFR 361.1(c)(2)].

a. An RDRC shall meet at least once each quarter during which research activity has been authorized or conducted. A quorum consisting of more than 50 percent of the membership must be present, with appropriate representation of the required fields of specialization. Our investigation indicates that approval of research is routinely granted, and research is allowed to commence, prior to review and approval by the RDRC at a meeting with a majority of the RDRC members present (i.e., a quorum). Examples include, but are not limited to, the following:

i. On November 30, 2009, the RDRC granted approval of Protocol **#(b)(4)**, titled "**(b)(4)**." However according to the minutes of the December 17, 2009, Quarterly Meeting, the full board did not meet to review Protocol **#(b)(4)** until December 17, 2009. Therefore, the RDRC approved research prior to review and approval by the RDRC at a meeting with a quorum.

ii. On March 19, 2008, the RDRC granted approval of Protocol **#(b)(4)**, titled "**(b)(4)**." However, according to the minutes of the March 26, 2008, Quarterly Meeting, the full board did not meet to review Protocol **#(b)(4)** until March 26, 2008. Therefore, the RDRC approved research prior to review and approval by the RDRC at a meeting with a quorum.

iii. On March 11, 2008, the RDRC granted approval of Protocol **#(b)(4)**, titled "**(b)(4)**." However, according to the minutes of the March 26, 2008, Quarterly Meeting, the full board did not meet to review Protocol **#(b)(4)** until March 26, 2008. Therefore, the RDRC approved research prior to review and approval by the RDRC at a meeting with a quorum.

b. At the March 26, 2008, meeting, the RDRC voted to approve Protocol **#(b)(4)**, titled "**(b)(4)**." However, less than a majority of members without conflicting interests was present. The RDRC meeting minutes for March 26, 2008, indicate that a quorum was initially met, with eight of thirteen voting members in attendance. However, four members (Dr. **(b)(6)**, Dr. **(b)(6)**, Mr. **(b)(6)**, and Mr. **(b)(6)**) abstained from voting on Protocol **#(b)(4)** due to conflicts of interest. If an RDRC member has a conflict of interest, then that member may only provide information requested by the RDRC, may not be counted toward the quorum, and may not vote on the proposed research in which he/she is conflicted. Therefore, abstention of these four RDRC members resulted in the loss of quorum, because only four of the thirteen RDRC members were available to vote. As a result, the RDRC approved research at a meeting without a quorum.

4. The RDRC failed to submit a special summary report to FDA immediately after approving research proposals which involve exposure of more than thirty research subjects [21 CFR 361.1(c)(3)].

Whenever a research proposal is approved that involves exposure of more than thirty research subjects, the RDRC shall immediately submit to the FDA a special summary of information in the format shown at 21 CFR 361.1(c)(3), "Report on Research Use of Radioactive Drug." The RDRC failed to submit special summaries to the FDA as required. Examples include, but are not limited to, the following:

- a. Protocol #(b)(4), titled "(b)(4)," was originally approved by the RDRC on December 4, 2009, to enroll forty subjects; however, no special summary was submitted to FDA.
- b. Protocol #(b)(4), titled "(b)(6)," was originally approved by the RDRC on March 10, 2009, to enroll seventy subjects; however, no special summary was submitted to FDA.

5. The RDRC failed to assure research was reviewed and approved by an institutional review board (IRB) [21 CFR 361.1(d)(9)].

An RDRC shall assure that investigators obtain the review and approval of an institutional review board that conforms to the requirements of 21 CFR part 56. Our inspection revealed that the RDRC failed to assure that research was reviewed and approved by an institutional review board. There was no documentation indicating that the RDRC requires that an IRB has reviewed and approved research, including in RDRC meeting minutes; and during our inspection, Dr. Brenner confirmed that the RDRC does not require documentation that an IRB has reviewed and approved research.

Our inspection revealed that the RDRC failed to protect the safety and welfare of human subjects, including a potentially vulnerable subject population (i.e., subjects with psychiatric disorders), because the RDRC failed to assure the necessary conditions described above, so that radioactive drugs used in research under their purview can be considered safe and effective.

The CUMC's written response to the Form FDA 483, dated June 6, 2011, promised significant changes to the operations of the RDRC. We note that written standard operating procedures (SOPs) for the RDRC are being developed in response to the FDA inspection. This response is inadequate because, even though the RDRC committed to

creating standard operating procedures, they did not include copies of the new SOPs or any projected completion date for these corrective actions. As a result, the FDA is unable to undertake an informed evaluation of the proposed corrective and preventative action's ability to prevent the recurrence of these or similar violations in the future.

This letter is not intended to be an all-inclusive list of deficiencies related to the RDRC.

The inspection of the RDRC identified serious regulatory violations that have an impact on the RDRC's protection of research subjects' safety. It is your responsibility to ensure that the Columbia University Medical Center RDRC's practices and procedures comply fully with all applicable statutes and regulations.

Within fifteen (15) business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Your written response should include any documentation necessary to show that full and adequate correction will be achieved. Please include the projected completion dates for each action. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

We recommend that you visit the FDA Web page indicated below for information on RDRCs that may assist you in your efforts to bring the CUMC RDRC into compliance with FDA regulations.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/1/Guidances/UCM163892.pdf>

We appreciate the cooperation shown to FDA Investigators Hansen, Steyert, and Fejka during the inspection. If you have any questions, please contact Patrick McNeilly, Ph.D., at (301) 796-2941; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Patrick J. McNeilly, Ph.D.
Acting Branch Chief
Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 2266
10903 New Hampshire Avenue

Silver Spring, MD 20993

Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

cc: David J. Brenner, Ph.D.
Chairman
Radioactive Drug Research Committee
Columbia University Medical Center
630 West 168th Street
VC 11, Room 230
New York, NY 10032

Links on this page:

1. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/>