DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 21, 2001

Mr. Edwin K. Zechman, Jr.
President & CEO
Children's National Medical Center
111 Michigan Avenue, NW
Washington, D.C. 20010-2970

Mark Batshaw, M.D.
Chief Academic Officer & Director of Children's Research Institute
Children's National Medical Center
111 Michigan Avenue, NW
Washington, D.C. 20010-2970

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1316
Research Project: CCG-0957 - A Limited Institution Phase I Study of B43-PAP Immunotoxin in Combination with Standard 3 Drug Induction for Patients with CD19+ ALL in Relapse
Principal Investigator: Gregory Reaman, M.D.

Dear Mr. Zechman and Dr. Batshaw:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed the Children's National Medical Center (CNMC) report dated January 14, 2000 regarding the allegations of possible noncompliance with the Department of Health and Human Services (HHS) regulations for protection of human subjects (45 CFR Part 46) involving the above referenced research. OHRP apologizes for the delay in its response.

In reviewing your January 14, 2000 report, as well as additional documents submitted by the complainant and the Food and Drug Administration (FDA), OHRP notes the following regarding the above-referenced research protocol:

(1) In a December 3, 1999 letter to the complainant, Dr. Reaman stated the following with regard to the treatment outcome of the subject F-12: "Although the bone marrow response at day 28 was coded as M1 (less than 5% leukemic blast cells), it was also noted to be profoundly hypocellular and since the ultimate cellular recovery of the bone marrow demonstrated only leukemic cell infiltration, this was not considered a successful outcome and has not been coded as such."

(2) In a December 6, 1999 response letter to OHRP regarding the complainant's allegation included in your January 14, 2000 report, Dr. Reaman reported the following:

> (a) "Verbal and written reports from clinicians at the Medical College of Virginia confirmed that the patient [F-12] experienced hypotension, which was felt to related to intravascular volume depletion as a result of capillary leak syndrome, a known side effect of this investigational agent. The patient responded to vigorous medical management and was assessed to have experienced grade III toxicity (capillary leak syndrome) as described in the protocol. Following the second infusion, verbal reports from physicians at the Medical College of Virginia and subsequent written reports confirm that the patient again experience hypotension related to capillary leak syndrome, which again responded to medical management. Both episodes necessitated brief admissions to the intensive care unit because of the degree of hypotension, but neither episode was considered life threatening and since the effects of the capillary leak syndrome recovered with medical management, it was considered to be grade III toxicity (as defined in the protocol), not severe, and did not require adverse event reporting."
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> (b) "Our evaluation of the research records of this patient as a result of this investigation revealed that a clerical error in reporting the grade of toxicity occurred; the toxicity was reported to the Operations Center of the Children's Cancer Group as grade II inadvertently, rather than grade III. This has been corrected."
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> (c) "The patient's [subject F-12] death occurred more than eights weeks following her

> last dose of investigational agent and more than six weeks after completion of the study protocol and following the administration of subsequent high dose chemotherapy, and, therefore, did not require reporting to the IRB or the Children's Cancer Group as an adverse event."

(3) In a January 14, 2000 response letter to OHRP regarding the complainant's allegation included in your January 14, 2000 report, John L. Sever, M.D., Ph.D., Chairman, CNMC Institutional Review Board (IRB), reported the following: "In reviewing the records of this protocol, this IRB found no evidence of noncompliance. CCG protocols do not report Adverse Events to the IRB when they occur thirty days or more after the last dose of study drug. The patient's death occurred more than eight weeks after the last dosage of investigational drug and more than six weeks after completion of the study. The Investigator was compliant in not reporting this information to the IRB. All appropriate information was reported to CCG. The error in coding of the toxicity as Grade II was corrected to Grade III."

(4) In a May 25, 2000 letter to Elaine Knowles Cole, Center for Biologics Evaluation and Research, FDA, regarding FDA's February 16, 2000 inspection of Dr. Reaman's conduct of the above referenced research, Dr. Reaman stated the following:

> (a) "We were cited for failure to ensure that the investigation was conducted according to the signed investigational plan, in that Appendix II of the protocol states that all subject deaths through 70 days post treatment are to be reported to the Data Safety Monitoring Board (DSMB). The FDA investigator indicated by telephone conversation with CBER that the death of subject F-12 was not reported to the DSMB. Appendix II of the subject protocol, CCG-0957, states that when deaths within 35 days of treatment: when a subject expires within 70 days after receiving an experimental agent on CCG-0957 or other monitored study, the treating physician will be asked to report the death within 24 hours of demise and to assess the role the experimental agent in the patient's demise (sic). This patient received multiple cycles of conventional chemotherapy, including vincristine and cytarabine as well as vincristine and etoposide one month later, not part of a monitored study; the requirement to report the death which occurred 55 days after receiving the investigational agent, B43-PAP, and which was in no way related to the investigational agent did not seem relevant.

This clearly represented a misunderstanding and not a conscious violation of the regulations. Furthermore, death notification through the cooperative group mechanism was followed in that death registration with the Children's Cancer Group Operations Office was accomplished when we were notified of the patient's death."

(b) "As also stated in the review, there was a discrepancy regarding progress reports. The explanation for this discrepancy was a simple clerical error. The 18 patients included in the progress report to the IRB on 3/15/97 should have been

included in the progress reports of 4/20/98 and 4/1/99, rather than 15. This correction has been made."

Based on its evaluation of the above reference documents, OHRP makes the following determinations:

(1) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) requires that any unanticipated problems involving risks to subjects or others be promptly reported to the IRB, appropriate institution officials, the Department or Agency head, and OHRP.

With regard to the allegations presented in OHRP's November 10, 1999 letter, OHRP finds that the adverse drug events experienced by subject F-12 during study participation did not meet the criteria for a reportable event under HHS regulations at 45 CFR 46.103(b)(5).

With regard to item (3) above, OHRP notes that subjects may experience delayed events more than 30 days after an intervention that represent unanticipated problems involving risks to subjects or others. In accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5), any unanticipated problems involving risks to subjects or others, even if occurring more than 30 days past final intervention, must be promptly reported to the IRB, appropriate institution officials, the Department or Agency head, and OHRP.

(2) HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. HHS regulations at 45 CFR 46.116(a) stipulate basic elements for such informed consent. OHRP notes the following:

The first paragraph of Section B. Procedure on page 2 of the approved informed consent document states: "*If you consent to this study* (emphasis added), you/your child will be

admitted to the hospital before beginning the B43-PAP treatment. A detailed medical history and physical examination will be performed. Prior to treatments, several blood specimens, a bone marrow aspirate specimen, and a urine specimen will be obtained. Multiple non-invasive laboratory evaluations (such as electrocardiography, echocardiography of heart, radiographic examination of chest) will be performed in order to determine the extent of your/your child's leukemia and general state of health." OHRP finds that Dr. Reaman failed to obtain the legally effective informed consent of subject

F-12 or this subject's legally authorized representative prior to the initiation of clinical procedures performed solely for the purpose of determining eligibility for participation in the CCG-0957 study. In specific, subject F-12 was admitted to a study-affiliated medical facility [Medical College of Virginia] on March 1, 1999 and underwent mandatory test procedures for determination of study eligibility as stated above on March 2 and 3, 1999. However, assent and legally effective informed consent was recorded in the study records as being obtained from the subject and the subject's parents, respectively, on March 4, 1999.

Required Action: By January 11, 2002, CNMC must submit to OHRP a satisfactory corrective action plan to address the above finding.

OHRP has the following additional concerns and questions:

(3) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. With regard to study CCG-0957, OPRR is concerned that the CNMC IRB has employed an expedited procedure to review changes that exceed this limitation. Specifically, a study modification request form was submitted on December 18, 1996 to the IRB Chairman that requested the following changes:

(a) a revision to allow study subject entry pending the results of the pulmonary function and HIV tests,

(b) a revision to allow informed consent to be signed and subjects to enter the study up to Day 7 of initiation of study therapy,

(c) the performance of an additional test prior to beginning B43-PAP administration to

verify adequate liver and kidney function, and

(d) the elimination of the prophylactic use of ibuprofen and pentoxifylline to decrease the likelihood of pericardial effusion.

An Institutional Review Board Report of Action dated December 19, 1996 and signed and dated by the IRB Chairman on March 24, 1997 stated: "The minor modification submitted for the protocol referenced above has been reviewed and granted Approval for Implementation. It is noted that the purpose of this modification is to: allow patient entry while pulmonary and HIV tests are pending; to perform a second test to ensure liver and kidney health; eliminate the use of ibuprofen and pentoxifylline from the protocol."

Additionally, OHRP is concerned regarding the discrepancy between the date of the Report of Action letter and the signature date of the IRB Chairman and the omission of reference to request (b) above from the summary portion of the letter.

Please respond.

(4) Continuing IRB review of research as required under 45 CFR 46.109(e) must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (i) the number of subjects accrued; (ii) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (iii) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (iv) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB. [see OPRR Report 95-01 on the OHRP web site at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm]

OHRP is concerned that the continuing review of ongoing research by the CNMC IRB may not be substantive or meaningful. In specific, it appears that from at least April 16, 1997 to May 19,

1999 nearly all protocols undergoing continuing review were neither individually presented nor discussed at the convened meetings of the CNMC IRB. In specific, OHRP notes the following:

> (a) A Progress Report Subcommittee (PRS) of the CNMC IRB reviews all protocols submitted for continuing review and presents a list of reviewed protocols for final review and voting by the CNMC IRB in a block format.
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> (b) At the IRB convened meeting of May 21, 1997, the progress report for study CCG-0957 was reported on the PRS list as deferred to the IRB Chair pending the following changes: "Incomplete - C. Risk and Benefit Analysis #3f was not answered; #3 a,b,c - the information is conflicting, what happened to the 3 subjects? Perhaps 3g should have been yes?? E. Modifications, this information is not provided in the summary as indicated." However, the Institutional Review
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> Board Report of Action to Dr. Reaman dated May 21, 1997 and signed and dated by the IRB Chairman on May 21, 1997 stated: "The IRB has reviewed and discussed the Progress Report submitted for the protocol referenced above [CCG-0957] on May 21, 1997 and voted unanimously to re-approve the study for continuation for 12 months."

Please respond in detail. In your response, please clarify whether the CNMC IRB has modified its continuing review procedures since 1999 to incorporate elements described under item (4) above. If continuing review procedures have not been so modified, CNMC should suspend immediately any Federally supported research projects (as well as any other research protocols covered by MPA M-1316) that were not eligible for an expedited review procedure and did not undergo substantive and meaningful continuing review by the convened IRB during the past one year period as described under item (4) above. For any project affected by this suspension, enrollment of new subjects must cease immediately except in extraordinary cases approved in advance by OHRP (OHRP would expect requests for approval of such cases to be rare). Furthermore, research activities involving previously enrolled subjects may continue only where the IRB finds that it is in the best interests of individual subjects to do so. For each affected protocol, this suspension must remain in effect until the protocol has undergone substantive and meaningful continuing review and been re-approved by the convened IRB.

By January 11, 2002, CNMC must submit to OHRP a list of all research activities which have been suspended as a result of this action.

(5) OHRP has the following concerns and guidance regarding the CNMC Policies and Procedures dated March, 1997 (Procedures).

(a) The second sentence in Section 2.4.1. Membership on page 11 of the Procedures states: "The RR-IRB [Rapid Response IRB] is made up of five regular member and four alternate members." OHRP notes that the current RR-IRB roster dated November 21, 2000 lists five regular members and *seven* alternate members. OHRP recommends that this section be updated to reflect the current RR-IRB membership.

(b) Item #1 of the *More than Minimal Risk* - No Direct Benefit section on page 16 of the Procedures should be revised to include the word "minor" before the word "increase", as required by 45 CFR 46.406(a).

(c) The first sentence in Section 3.5.2.7 Questions on page 27 of the Procedures that must be included in all informed consent forms approved by the IRB, states: "The IRB has reviewed this study, evaluated the potential benefits and risks, and has granted approval for the solicitation of participants." OHRP is concerned that the inclusion of this explicit statement in an informed consent document may induce potential subjects not to evaluate the study for themselves.

(d) Section 4.1.1 Subcommittee to Review CCG/ACTU Protocols on page 39 of the Procedures describes the operational details of a subcommittee of the CNMC IRB that meets monthly for the initial review of these protocols prior to the scheduled IRB meetings and makes recommendations to the CNMC IRB regarding these particular protocols. OHRP notes that an independent IRB entitled "Special IRB" was established by CNMC to primarily review multi-center protocols on October 23, 1998. This section should be revised to include a description and operational details of this Special IRB.

(e) Under Section 4.5 Expedited Review on page 48 of the Procedures, please note that list of categories of research that may be reviewed by an IRB through expedited procedures was updated by OPRR and FDA in the Federal Register on November 9, 1998 (63 FR 60364). The list is available on the OHRP web site at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm

(f) Section 7.1. Notifications on page 56 of the Procedures should be revised to add HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) that require reporting to the IRB, appropriate institutional officials, and the Department of Agency head and OHRP of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(6) OHRP notes that the IRB meeting minutes from 1996 -1998 frequently document the approval of research involving children. 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.

By January 11, 2002, please submit to OHRP CNMC's response to the above concerns. Please provide to OHRP any revised or updated written IRB policies and procedures.

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,

Robert J. Meyer
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mr. Ron Sloan, CNMC
Dr. John L. Sever, CNMC
Dr. Gregory H. Reaman, CNMC
Commissioner, FDA
Dr. David A. Lepay, FDA
Dr. James F. McCormack, FDA
Ms. Elaine Knowles Cole, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey M. Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Janice F. Walden, OHRP
Mr. Barry Bowman, OHRP