DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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February 28, 2005

Richard B. Johnston, M.D.
Executive Vice President for Academic Affairs
National Jewish Medical and Research Center
1400 Jackson Street
Denver, Colorado 80206

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 778

Research Projects:
(1) Beryllium Disease Natural History and Exposure Response (HS-1360)
(2) Cytokine Regulation of Environmental Lung Disease (HS-1361)
(3) Study of T-Cells and Genetics in Granulomatous Disease (HS-1367)
(4) Pathogenic T-Cells in Chronic Beryllium Disease (HS-1393)
(5) Beryllium: Exposure, Immune and Genetic Mechanisms (HS-1626)
(6) Dose of Beryllium Causing Beryllium Sensitization and Disease (HS-1362)

Investigators: Lee S. Newman, M.D. and Lisa A. Maier, M.D.

Research Project:
(7) Beryllium Medical Surveillance at a Former Nuclear Weapons Facility During Cleanup Operations (HS-1745)

Investigator: Holly M. Sackett

Dear Dr. Johnston:

The Office for Human Research Protections (OHRP) has reviewed National Jewish Medical and Research Center's (NJMRC) January 21, 2004 report that was submitted in response to OHRP's December 10, 2003 letter to NJMRC, regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

Based upon its review of NJMRC's January 21, 2004 report, OHRP makes the following determinations regarding the above-referenced research:

(1) In its December 10, 2003 letter, OHRP presented the allegation that the investigators for the above-referenced research failed to obtain the legally effective informed consent of the subjects or the subjects' legally authorized representatives, as required by HHS regulations at 45 CFR 46.116. Specifically, it was alleged that the investigators failed to obtain the legally effective informed consent from subjects who provided tissue samples in the Department of Environmental and Occupational Health Sciences (DEOHS) specimen banks, or blood samples for genetic phenotyping. In addition, it was alleged that research procedures involving bronchoscopy and arterial blood draws were unwittingly performed on subjects who believed these procedures were solely for clinical purposes, and extra tissue was collected for research purposes during clinical evaluations.

(a) NJMRC's January 21, 2004 report stated the following:

"The Review Committee reviewed the consent form files for all six of the protocols. A total of 552 unique subjects enrolled in the six protocols. These 552 subjects completed 2156 different consent forms. There were no missing consent forms for any of the 552 subjects. Overall, we found almost 100% compliance with the consent form process. The only discrepancies identified were:

- One (1) consent form was missing the signature page. The subject initialed all other pages but the last page of the form was missing.
- Two (2) consent forms were missing the subject's signature. The subject initialed all of the pages of the consent form but the final signature was not obtained."

"A process is in place to prevent clinical specimens from unknowingly being used for research purposes without first obtaining consent.

Specimens received in the research lab are crosschecked [*sic*] with the research database prior to the specimens being used for research. If consent is not confirmed then the specimen is destroyed and not used for research."

"The physicians, in all but a few situations, do not participate in the research consenting process with their patients. The physicians are concerned that if they obtain the research consent, there is the potential to confuse the patient that participation in a research protocol is in some way connected to the patient care responsibilities/relationship. Consent for research protocols is handled by research staff that have no patient care responsibilities."

"Patients/subjects are re-consented every time they are scheduled for another procedure. Typically patients are scheduled for follow-up visits on a 1-2 year schedule. If a bronchoscopy with lavage and/or blood work is clinically required on the follow-up visit, the patient is asked to sign a new consent form for these procedures. At this time the patient may agree or refuse to participate in the research protocol."

"Patients undergoing a clinical bronchoscopy with lavage and who consent to participate in the research protocol sign two consent forms. The patient/subject sign [*sic*] the standard hospital clinical consent used for all patients having a bronchoscopy. They also sign a research consent form approved by the IRB. The research consent makes it clear that the medical procedures are part of the patient's regular medical care. The consent goes on to explain that the patient's specimens will be used for research purposes only after all clinical needs are met."

"Patients/subjects who consent to have a non-clinical bronchoscopy performed solely for research purposes sign a different research consent form. This research consent form clearly states that there is no clinical purpose for the bronchoscopy and it is being done only for research purposes. These subjects are also compensated for their research participation. The informed consent process is clear that the subject's participation is unrelated to their clinical care, that the subject will receive no personal benefit, and participation is voluntary."

"No biopsy tissue is used in these protocols. Research blood specimens are drawn simultaneously with clinical specimens. The researchers only have access to blood specimens and excess lavage specimens."

"Patients are asked to allow additional blood to be drawn for inclusion in the protocol(s). The blood draws are already being done for clinical purposes and only if the patient consents is additional blood (~25 ml) collected for research purposes. *(These draws are venous draws not arterial*...[emphasis in original]*)."*

"For other than a small number of pure research bronchoscopies these procedures are all being performed for clinical purposes. Of the 543 subjects enrolled in the five Beryllium protocols, 42 of these (8%) consented to having bronchoscopies performed solely for research purposes. A total of 51 research bronchoscopies were performed on these 42 subjects."

(b) The NJMRC Institutional Review Board (IRB)-approved informed consent document entitled "Part One - Procedural Consent Form for Research Participation" for the above-referenced research projects (1)-(5) stated the following:

"**DESCRIPTION OF RESEARCH PROCEDURES**
If you have CBD, BeS or sarcoidosis you will be undergoing a routine clinical evaluation.... The procedures involved in clinical evaluation or medical surveillance are part of your regular medical care and not part of this research study."

"**Use of blood and/or BAL cells:** A bronchoscopy with bronchoalveolar lavage and biopsy may be part of your routine clinical evaluation and necessary for diagnosis. You will sign a separate clinical consent form for this procedure. We request your permission to reserve cells and other substances from this procedure for research studies that will be explained in Part Two. Using left over [*sic*] cells does not change the procedure in any way."

"**STORAGE OF SAMPLES**
Your blood and/or BAL cells from this blood draw or bronchoscopy will be used for the research studies described in Part Two. If any sample is

left over, we request your permission to save the cells, other materials, and biopsy tissue for future studies of CBD.... Your stored samples may be shared with other hospitals or research institutions after your name and other identifying information has been separated from them.... You may request withdrawal and destruction of your specimen at any time so that no further analysis will be done."

"I give permission for my blood, lavage materials and biopsy specimens to be stored for at least 20 years in the investigator's laboratory for future use in studies of chronic beryllium disease."

(c) The NJMRC IRB-approved informed consent document entitled "Part One - Procedural Consent Form for Research Participation and Research Bronchoscopy" for the above-referenced research projects (1)-(5) stated the following:

"**DESCRIPTION OF RESEARCH PROCEDURES**
If you have CBD, or sarcoidosis [*sic*] you will be undergoing a routine clinical evaluation.... The procedures involved in clinical evaluation are part of your regular medical care and not part of this research study."

"**Research Bronchoscopy:**
If you have CBD, sarcoidosis, or are a healthy volunteer, you may be asked to voluntarily undergo a bronchoscopy with BAL for research. If conducted for research, these procedures are not related to your clinical care and will be paid for by the study."

(d) The NJMRC IRB-approved informed consent document entitled "Part Two - Informed Consent Form" for the above-referenced research project (5) stated the following:

"**PROCEDURES**
Participation in this study involves a medical record review, a questionnaire, and a blood draw (up to 50 ml). If you are not undergoing a bronchoscopy for clinical purposes, you may be asked to do so for research. If you have a bronchoscopy, and you have agreed to allow us to store your samples (Part One), we will store any BAL cells that are not used immediately. These samples may be used for this and later studies."

> "**GENETIC TESTING**
> The study doctors are asking your permission to perform genetic testing on your blood and/or BAL cells. The purpose of this testing is to examine the genetic basis of CBD.... The findings of the genetic tests are considered research and are not the same as 'genetic testing' results performed in clinical diagnostic laboratories.... None of these results will be part of your medical record.... Your samples will be used to study CBD only. Your name and other identifying information will be separated from the samples before they are sent for genetic testing. Neither genetic information about you nor other information obtained from your sample will be given to you, your family, your doctor, or other third parties. You may request withdrawal and destruction of your specimen at any time so that no further genetic analysis will be done."

Based on the statements in (1)(a) - (d) above and its review of other information presented in your report, OHRP finds that, excepting the three informed consents stated in (a) above, the allegation that the investigators failed to obtain the legally effective informed consent from subjects for the above-referenced research projects (1)-(6) was not substantiated. OHRP also finds that (i) the protocols specified only the use of additional venous blood specimens for the above-referenced research projects (1)-(6), and excess clinical BAL specimens for research purposes for the above-referenced research projects (1)-(5); (ii) the informed consent documents contained statements that clearly differentiated between the performance of clinical and research bronchoscopies and discussed the possible use of collected specimens for future research; and (iii) the bronchoscopies performed for the above-referenced research projects (1)-(5) were deemed appropriate for either clinical or research purposes. Accordingly, OHRP finds that the remaining allegations noted above were not substantiated.

Corrective action: With regard to the incomplete documentation of informed consent noted in (1)(a) above, OHRP notes NJMRC's plans to emphasize the importance of complete informed consent documentation with all principal investigators and research staff, and to conduct additional audits of other research to ensure compliance with this requirement.

(2) It was alleged that the investigators failed to provide a description of the reasonably foreseeable risks or discomforts of the research to the subject, as required by HHS regulations at 45 CFR 46.116(a)(2). In specific, it was alleged that Dr. Newman instructed an employee to misrepresent the risks associated with the research.

NJMRC's January 21, 2004 report stated the following:

> "The Review Committee asked the research staff if they were aware of anyone being instructed to '*misrepresent*' [emphasis in original] risk. All of the interviewed staff stated that, to their knowledge, this has never happened. We reviewed the consent forms, both clinical and research, to determine if risks were well described. From this review it appears that the risks of undergoing the bronchoscopy are well represented in the consent forms."
>
> "After completing the staff interviews the Review Committee could not find any evidence that Dr. Newman in any way instructed an employee to misrepresent the risks of procedures associated with these protocols."

Based on the statements above and its review of other information presented in your report, OHRP was unable to make a determination regarding the above allegation.

(3) It was alleged that the investigators failed to ensure the privacy of subjects and maintain the confidentiality of data, as required by HHS regulations at 45 CFR 46.111(a)(7). In specific, it was alleged that data security for the above-referenced research projects (1)-(6) was lax, and that students are given access to subject identifiers on request.

NJMRC's January 21, 2004 report stated the following:

> "The access to the subject electronic databases is limited to those involved in the protocols. Staff must first have a network password that allows them to access the servers where the data reside. Individual databases are then secured by another password.... Database information is de-identified as soon [*sic*] and whenever possible and those who have no need to know subject identity are not provided to the level of information."
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> "Paper records are kept in locked file cabinets within lockable rooms.... The physical surroundings where the paper records are kept are secure and isolated from individuals gaining unauthorized access. Only one employee has a key to the files and the files are locked when not in use."
>
> "The issue of students being given access to subject identifiers upon request could not be supported. We asked this of all the staff and principal investigators involved and were told this is not the case. If students are

> given access to protected data they follow the same guidelines used for employees. Students must be trained and their access must be consistent with the permitted use of the data. National Jewish is an educational institution and at any given time may be involved in any number of educational programs. When students are involved, National Jewish expects the same level of training, supervision, and confidentiality that is required of National Jewish employees. If there were confidentiality breaches the Review Committee could not identify them."

Based on the statements above and its review of other information presented in your report, OHRP finds that the above allegation was not substantiated.

(4) It was alleged that the investigators failed to submit changes to the protocol to the NJMRC IRB, as required by HHS regulations at 45 CFR 46.103(b)(4)(iii). In specific, it was alleged that the investigators failed to amend the research to reflect personnel changes.

NJMRC's January 21, 2004 report stated the following:

> "This concern was reviewed with all the involved staff, including the IRB manager.... In reviewing modifications to consent forms, personnel changes, when required, were noted to have occurred. The IRB manager was unaware of any instances where required personnel changes were not forwarded to the IRB. Though it is not possible to say with certainty, the Review Committee could not find any circumstances where proper notification did not occur."

Based on the statement above and its review of other information presented in your report, OHRP finds that the above allegation was not substantiated.

OHRP finds that NJMRC's corrective action plans adequately address the finding noted in (1) above and are appropriate under the NJMRC Assurance.

(5) It was alleged that the investigators failed to obtain approval from the NJMRC IRB prior to initiating a research study, as required by HHS regulations at 45 CFR 46.103(b) and 46.109(a). In specific, it was alleged that a student conducted the above-referenced research project (7) that involved accessing an existing database without IRB approval after being instructed by Dr. Newman not to submit the protocol to the IRB.

(a) NJMRC's January 21, 2004 report stated the following:

> "In the spring of 2003 [*sic*] a graduate student did work on a project for her masters thesis that involved accessing a database at National Jewish. The project involved a service contract between National Jewish and DynCorp of Colorado, Inc."
>
> "The graduate student worked under the direction of Dr. Newman in analyzing this data for the company and at the same time the project helped her satisfy her degree requirements.... When the student started the project it was not considered to be a 'research project.'"
>
> "The question associated with this concern is one of timing. The student's project did not start out as a research project and therefore IRB approval was not anticipated. The project was part of a service contract that <u>did not</u> [emphasis in original] involve research subjects. As represented by the student, her project was not anticipated to be a publishable project until late in the spring semester. She was advised to check with the IRB and did so once she anticipated publishing her project. The students's IRB approval application is dated May 5, 2003 and the IRB approved the project on May 9, 2003. We find no indication that Dr. Newman told the student to not submit the project to the IRB. The student told us that Dr. Newman instructed her to go to the IRB to see if approval was necessary and she promptly did so."
>
> "The Review Committee's findings were that the IRB approval was sought and given when the project was considered for publication. This is consistent with National Jewish policy. The Review Committee cannot determine beyond a doubt that the student considered publication significantly before IRB approval was requested. However, there is no indication that IRB processes were in any way being intentionally circumvented."

(b) Section A. Scope of Authority in the NJMRC IRB Policy entitled "Authority-Institutional and IRB," dated December 17, 2003, states the following:

> "National Jewish IRB review and approval is required for any research involving human subjects that is conducted by National Jewish faculty, staff, or students. IRB review and approval is required for research that is

conducted by or under the direction of any employee or agent of National Jewish, in connection with his or her National Jewish responsibilities. The geographic location of the study and the funding status of the study do not affect the requirement for National Jewish review and approval. Studies that must be submitted for IRB review include but are not limited to:

1. Any activity that meets the definition of human subject;
2. Use of "waste" or "extra" human tissue or fluids;
3. **Research on medical records** [emphasis added];
4. Collection of data through surveys or observation;
5. Research use of non-investigational drugs or devices; or
6. Investigational drugs or devices."

(c) The April 1, 2003 Memorandum from Lisa Polisher, Data and Safety Monitoring Coordinator and Research Subject Advocate, NJMRC IRB, to Richard Meehan, M.D. and Henry Milgrom, M.D., Co-Chairs, NJMRC IRB, stated the following:

"Holly Sackett came by to ask me some questions about the need for IRB approval. She is a graduate student at UCHSC (Preventive Medicine Program, MSPH). Her thesis advisor is Lee Newman, MD, in the Division of Environment and Occupational Health Sciences. A co-worker recently informed her that she might need IRB approval of her research prior to publication."

"According to Holly, during the preliminary stages of her thesis work, Dr. Neuman informed her that she did not need IRB approval because he would be providing her with existing data on which to do her thesis work. Dr. Neuman gave Holly access to the 'Current Worker' database. This database contains subject names, among other identifiers. Holly has been working with this database since June, 2002 but is not certified to conduct human subjects research through National Jewish IRB or COMIRB."

"Holly's thesis is now complete and due to be turned in to UCHSC by May 1, 2003. Holly is scheduled to defend her thesis on April 16, 2003 and then plans to submit her paper for publication. Had she submitted a proposal prior to conducting her research, it might have qualified for an exemption if the data were de-identified. This protocol would likely have

> qualified for a waiver of informed consent without de-identifying the data. **There are no provisions in the regulations for retroactive approval** [emphasis in original]."

(d) The April 2, 2003 Memorandum from Richard Meehan, M.D. to Lisa Polisher and Henry Milgrom, M.D. stated the following:

> "Henry [Dr. Milgrom] and I have faced similar situations before especially when investigators are ready to publish retrospective clinical studies as they were unaware that a waiver of consent was to granted [*sic*] by IRB before the study was to be started (chart reviews or radiology studies). It would be inconsistent to take a more punitive action on this study since the PI (graduate student) did not knowingly violate IRB policy and sought advice from her mentor."
>
> "Please have another memo sent to all clinical faculty signed by me, Henry and Dr. Crapo [James D. Crapo, M.D., NJMRC Institutional Official at that time] reminding PIs that they are not authorized to share existing patient data without IRB approval and patient confidentially [*sic*] issues must be honored by having IRB approval prior to non-treating physicians viewing patient charts for clinical studies."

(e) Section (8) of the NJMRC IRB Requirements for Research Approval Form signed by Ms. Sackett and dated May 5, 2003 for the above-referenced research project (7) stated the following:

> "Inclusion Criteria.
> The study population consists of 2,381 beryllium-associated workers who (1) were hired by any contractor or subcontractor to work at the facility; (2) agreed to participate in the Chronic Beryllium Disease Prevention Program; and (3) completed informed consent for this program; and (4) completed a health and exposure history questionnaire between October 1998 and August 2002."

Based on the statements above and its review of other information presented in your report, OHRP finds that Ms. Sackett conducted a nonexempt research project for her master's thesis that involved accessing a database of identifiable health records of beryllium-associated workers prior to obtaining NJMRC IRB approval, in contravention of HHS regulations at 45 CFR 46.103(b) and 46.109(a). OHRP notes that whether a research

activity is conducted (i) concurrently with a service contract agreement or (ii) absent consideration for future publication is not sufficient to justify a determination that such research activity does not constitute research under HHS regulations at 45 CFR part 46.

Required action: By April 8, 2005, NJMRC must submit to OHRP a satisfactory corrective action plan which addresses the findings stated above. The plan should address procedures to ensure that similar nonexempt research receives prospective IRB review and approval.

At this time, OHRP would like to provide the following guidance:

(6) Convened IRBs often set conditions under which a protocol can be approved. When the convened IRB requests substantive clarifications or modifications to the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research should be **deferred** pending subsequent review by the convened IRB of responsive material.

(7) 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, and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB chair or another IRB member designated by the chair, continuing review must occur no more than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date on which the IRB chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP appreciates the commitment of NJMRC 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: Dr. Lynn M. Taussig, President, NJMRC
Dr. Richard B. Meehan, IRB Chair, NJMRC
Ms. Mary E. Travis, IRB Administrator, NJMRC
Commissioner, FDA
Dr. David A. Lepay, FDA
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Ms. Shirley Hicks, OHRP
Ms. Patricia El-Hinnawy, OHRP
Ms. Janet Fant, OHRP