JEFF BINGAMAN
NEW MEXICO

703 HART SENATE OFFICE BLDG.
WASHINGTON, DC 20510–3102
(202) 224–5521
IN NEW MEXICO—1–800–443–8658
TDD (202) 224–1792
senator_bingaman@bingaman.senate.gov

United States Senate

July 1, 2005

The Honorable Mike Leavitt
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Leavitt:

I am writing to express great concern about the "Anthrax Vaccine Clinical Trials" registered on the ClinicalTrials.gov website as beginning on September 4, 2004, and currently enrolling patients. According to the registration, the National Institutes of Health (NIH) study will include 350 adult volunteer and 100 children in first and second grade to receive either a new vaccine "produced by genetic engineering, protective antigen (rPA) or a human vaccine from 1970." The purpose is to test the comparative efficacy of the two vaccines.

I, first of all, hope that the Department will take immediate action to update the information on the website to indicate the actual current status of the anthrax vaccine use by members of the military. Currently the public receives, through the site, the information that "the rising prospects of B. anthracis being used as a weapon have led to routine administration of the anthrax vaccine to members of the armed forces." The fact is that U.S. District Court Judge Emmet G. Sullivan issued a permanent injunction against the military's mandatory vaccination program in October 2004 because he found the vaccine had not been properly licensed for use against inhalation anthrax. To ensure that members of the public, who may be interested in this clinical trial, are correctly informed, this revised information should be included in ClinicalTrials.gov and the NIH website (Protocol Number: 04-CH-0283).

Given the concerns expressed by Judge Sullivan regarding the Food and Drug Administration's (FDA) inadequate regulation of the Anthrax Vaccine Adsorbed (AVA) and other criticisms of that vaccine over the years, the need for clinical trials to evaluate the safety and effectiveness of various anthrax vaccines certainly makes sense. Indeed, as Stewart Simonson, Assistant Secretary in the Office of Public Health Emergency Preparedness at the U.S. Department of Health and Human Services (HHS) has said, "Due to limitations inherent in the currently available anthrax vaccine, there is consensus in the scientific community about the need to develop and acquire a next-generation anthrax vaccine…."

However, I have grave concern about any intent to proceed with clinical trials with children at this point. As the study summary reads, "This is the first study of our investigational rPA vaccine in humans. The broad objectives are to characterize the safety and serum antibody levels of anti-PA. Phase 1 and Phase 2 studies, safety and immunogenicity of 2 dosages and 3 formulations of rPA, involving 350 adult volunteers and 100 first and second graders are

planned. The optimal dosage and formulation, determined in the phase 1 study, and AVA (Anthrax Vaccine Adsorbed) will be administered to 100 first and second graders on a random basis."

Surely considerable information regarding the safety of the new vaccine, as well as about its potential effectiveness, should be obtained in adults long before any consideration is given to providing it to children. And, based on what already is known about the adverse event profile of the older vaccine, it should not be "tested" in children at all.

Recent articles in the *Hartford Courant* (June 23, 2005) and *Kansas City Star* (June 27, 2005) indicate that NIH is not planning for the study on children to occur "until the vaccines are fully tested on 350 adults and shown to be safe for them." I hope you will confirm that is the case.

Even if that is true, however, it appears that children would then be subjected to Phase II clinical trials involving a new investigational vaccine along with a vaccine that has been linked to over 1,200 illnesses in our nation's military personnel, according to a government report, and several reported deaths (*Las Vegas Sun, "More Than 1,200 Who Had Anthrax Vaccine Now Sick,"* June 16, 2005). Even beyond that crucial safety issue is the question of the unknown effectiveness of the new vaccine, and thus, of its unknown potential benefit for children.

With that in mind, it becomes particularly difficult to see how the risk of such research on children for either vaccine can be deemed ethical, particularly when the research does not offer the prospect of direct benefit.

The Institute of Medicine's report *Ethical Conduct of Clinical Research Involving Children* (2004), which I requested as part of the "Best Pharmaceuticals for Children Act of 2002" (P.L. 107-109), points out, "...when proposed research involves a minor increase over minimal risk and does not offer the prospect of direct benefit, the research must be limited to children with a disorder or condition *and* must be expected (among other criteria) to generate vital knowledge about the disorder or condition" (45 CFR 46.406; 21 CFR 50.53).

The IOM report adds, "For research that involves a control group of healthy children (and the anthrax study is to include healthy children) without a disorder or condition and without prospect of direct benefit from the research, the research procedures for that group would have to involve no more than minimal risk."

Subpart A of the HHS regulation define "minimal risk" as meaning "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102(i); 21 CFR 50.53(k)).

It is important to note that, first, the FDA in 2002 required revision of the AVA product label to include approximately 40 serious adverse events. As the product label for AVA now reads, "Approximately 6% of the reported events were listed as serious. Serious adverse events include those that result in death, hospitalization, permanent disability or are life-threatening." Further,

the FDA raised the rate of systemic reactions by up to 175 times over what had been listed on the previous 1999 product label, from 0.2% to 5-35%.

Similarly, the label was revised to upgrade from a "possible risk" to a "known risk" to pregnant women because of "positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans."

Based on this and other information, including the fact that the Advisory Committee on Immunization Practices and the Armed Services Epidemiology Board said the evidence "strongly favors" the belief the vaccine led to the death of Rachel Lacy, a 22 year-old reservist from Illinois back in 2003, this vaccine can hardly be deemed to be creating a "minimal risk" no greater than that encountered by children in everyday life or in a routine physical examination. Nor would it appear to be a "minor increase over minimal risk."

Even if the risks were deemed to be minor, however, ethical standards require that only children with relevant disorders or conditions be exposed to slightly more than minimal risk – without prospect of direct benefit – to "gain important knowledge about those disorders or conditions." No children in this country have been exposed to inhalation anthrax. I question, therefore, what possible justification was used by the relevant Investigational Review Board (IRB) to approve such a clinical trial in children?

Did the IRB that reviewed the protocols for this anthrax vaccine clinical study include, as recommended by the IOM, "at least three individuals with [expertise in child health care and research] present as members or alternates during meetings in which a research protocol involving children is reviewed"? If so, who were those individuals?

Furthermore, did the IRB approve informed consent documents that are to be provided to the adult human subjects and the parents or guardians of the children in the trial? If so, please provide me a copy of those informed consent documents for both adult and child test subjects.

In addition to the grave concerns I have about children participating in this clinical trial, I am also deeply concerned about the expenditure of billions of dollars on clinical trials and vaccine procurement in this area with little or no coordination among various federal departments, including internally at HHS.

On May 24, 2005, Dr. Donna Knutson of the Centers for Disease Control and Prevention (CDC) testified before the Defense Forum Foundation that the CDC is creating $1 billion in a stockpile of antibiotics for an anthrax attack that would cover 60 million Americans for 60 days. She also testified that the CDC is working with the Department of Defense (DoD) and spending $16 million annually on research and clinical trials, as recommended by the IOM in another report entitled *An Assessment of the CDC Anthrax Vaccine Safety and Efficacy Research Program* to "largely address the challenge of determining immunologic correlates of protection and documenting the efficacy of the vaccine." Although these studies were funded for the past few years, Dr. Knutson testified that "I don't think that the anthrax vaccine studies are being funded or proposed in the '06 budget." There is a seeming disconnect within the Department as to what research should and should not be conducted with respect to the anthrax vaccines.

Further indication of this disconnect in the Administration is the stark contrast between the HHS expenditure in the past few months of $878 million and $123 million on the purchase and procurement of the rPA and AVA vaccines, respectively – prior to the safety and efficacy studies – and the DoD failure to seek the $5 million needed to keep in operation the Vaccine Healthcare Center (VHC) Network, currently the only organization dedicated to providing treatment, educational tools and case management efforts for our nation's military personnel who have suffered adverse reactions to the anthrax and smallpox vaccines.

Finally, my office is also hearing that the NIH study referenced in this letter is of a different experimental rPA vaccine than that which HHS has already been contracted for from VaxGen. If this is correct, why did the government commit nearly $878 million for an experimental rPA vaccine that has only passed Phase 1 clinical trials when, based on the NIH study, your researchers believe they can develop better rPA vaccines?

I was a cosponsor and strong supporter of both the "Best Pharmaceuticals for Children Act of 2002" (P.L. 107-109) and the "Pediatric Research Equity Act of 2003" (P.L. 108-155) and fully recognize the necessity of clinical research involving children. However, I asked for the IOM study on the adequacy of ethical safeguards for children to be included in that legislation. As the Senate Report 107-079 to the "Best Pharmaceuticals for Children Act" said, "The pediatric exclusivity provision has increased significantly the number of drug studies conducted in children. This increase, coupled with reports of unrelated incidents that have raised concern about human subject protection, has led some to request a thorough examination of safety and ethical controls on pediatric studies. The committee shares the concern that the ethical conduct of pediatric research and the safety of children be paramount."

The IOM study resulting from that legislation adds, "Meeting the special ethical and legal standards for protecting infants, children and adolescents who participate in research demands additional resources and attention beyond that required for protecting adults…In some cases, the special ethical and regulatory protections for children may preclude potentially important clinical studies that would be approved for adult participation."

I ask that both the NIH and FDA, as appropriate, please review these very important issues and respond to the questions I raise in this letter at their earliest convenience. Thank you for your consideration of this important matter.

Sincerely,

Jeff Bingaman
U.S. Senator

xc: Dr. Elias Zerhouni
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Lester Crawford, D.V.M., Ph.D.
Acting Commissioner
U.S. Food and Drug Administration
5600 Fisher Lane
Rockville, MD 20857

Dr. Julie Gerberding
Director
Centers for Disease Control and Prevention
1600 Clifton Avenue
Atlanta, GA 30333

Dr. Duane Alexander
Director
National Institute of Child Health and Human Development (NICHD)
9000 Rockville Pike
Bethesda, MD 20892