United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

March 13, 2006

Via Electronic Transmission

The Honorable Michael Leavitt
Secretary
U.S. Department of Health & Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Leavitt:

I write you today because you have full authority, as the Secretary of the Department of Health and Human Services (Department/HHS), over the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP). During the past few years there has been an undeniable absence of strong leadership at the FDA. Consequently, it is an agency that appears to be constantly in crisis. The ability of the FDA to act promptly and consistently to protect the public health and to help the public get accurate, science-based information has been called into question once again. Accordingly, I respectfully request your full and immediate attention to the issues raised here. I sincerely hope you also recognize the real world consequences of the leadership void at FDA.

For instance, in a meeting last Friday OHRP, officials told my staff on the Committee on Finance (Committee) that it is the considered position of OHRP that an ongoing, FDA-approved clinical trial is unethical.[1] The experimental product, a blood substitute manufactured by Northfield Laboratories Inc. (Northfield) called PolyHeme, is presently being tested in 18 states across the United States. The FDA approved this experiment (the PolyHeme Study) under a federal regulation promulgated to allow for an emergency research exception to informed consent in human studies, if specific criteria are met (Emergency Research Consent Exception).[2] Last week, I requested, as chairman of the Committee, all correspondence between OHRP and FDA related to the PolyHeme Study. On short notice, OHRP officials briefed my Committee staff on the ethical issues associated with the PolyHeme Study. The intra-Department correspondence provided to the Committee, including formal letters and internal e-mail, shows that OHRP has long been urgently concerned about the PolyHeme Study. At the end of last week, OHRP officials told my Committee staff that after FDA asserted exclusive jurisdiction over the PolyHeme Study, OHRP expressed its urgent concerns to FDA officials over the course

1 OHRP's Director advises the HHS Secretary on issues of human subject protections, serves as the Executive Secretary of the Secretary's Advisory Committee on Human Research Protections (SACHRP), and OHRP provides technical and logistical support to the SACHRP.

2 21 C.F.R. 50.24

of a year and a half. These urgent concerns were raised to the Acting FDA Commissioner and to the Assistant Secretary level within HHS. According to the Director of OHRP and his staff, this was the first and only time OHRP had to formally elevate its urgent concerns to the level of the FDA Commissioner. These same officials stated that OHRP would not have approved the PolyHeme Study because its design and implementation remains unethical.

OHRP articulated three primary concerns with the PolyHeme Study: (1) the in-hospital phase of the study is unethical, i.e., informed consent is not being obtained from patients who continue to receive PolyHeme once blood is available in the emergency room; (2) the community consultation failed to accurately describe the PolyHeme Study because it emphasized the ambulance phase and de-emphasized the in-hospital phase of the PolyHeme Study; and (3) the community consultation and public disclosure associated with the PolyHeme Study underestimated the potential risks and overestimated the benefits of PolyHeme. The potential benefit of a viable blood substitute is not an issue in dispute here. However, as chairman of the Committee, I also question whether or not it is ethical to withhold blood from trauma patients in a hospital setting in favor of an experimental product, without their consent. How the FDA implemented the Emergency Research Consent Exception for the PolyHeme Study is also of paramount concern.

Prior to contacting OHRP, I wrote to the FDA's current Acting Commissioner, on February 23, 2006, after a number of serious allegations came to the attention of the Committee, suggesting the regulatory criteria under the Emergency Research Consent Exception may not have been met fully and meaningfully in the PolyHeme Study. As the old proverb goes, "the devil is in the details." My Committee staff are presently reviewing the approval and conduct of the PolyHeme Study, including but not limited to the FDA's implementation of its Emergency Research Consent Exception, the FDA's role in approving the study, whether or not mortality and adverse events were promptly disclosed to the FDA, the FDA's ongoing oversight of the study, and whether or not the public has been fully informed about the risks and benefits of the PolyHeme Study.

I am personally troubled that, for all intents and purposes, the FDA allowed a clinical trial to proceed, which makes the inhabitants of 32 communities in 18 states, and anyone living or traveling near these communities, potential "guinea pigs," without their consent and, absent consent, without full awareness of the risks and benefits of the blood substitute. As a United States Senator representing the State of Iowa and as chairman of the Committee with jurisdiction over the Medicare and Medicaid programs, I am responsible for oversight of matters that affect my constituents and the beneficiaries of these federal health care programs. The idea that the FDA would put the burden on the public to opt out of this experiment is outrageous. Equally outrageous is the FDA's apparent failure to ensure that communities are fully aware of the risks, benefits, and nature of this experiment. Accordingly, my letter to the Acting Commissioner requested that the FDA immediately provide the public with more meaningful information about the PolyHeme Study. In addition, I requested that the FDA brief my Committee staff by March 8, 2006. However, the FDA stated that there were difficulties in coordinating and scheduling a briefing by this deadline. The FDA informed my Committee staff that FDA officials would not be available for a briefing until Wednesday of next week, which is now the scheduled date.

My requests to the FDA did not seem unreasonable to me, especially given the serious nature of the ethical and safety issues involved with the PolyHeme Study. However, the FDA has yet to provide more information to the public on the PolyHeme Study, which is no surprise given that the FDA has been slow to address numerous other real and potential drug safety issues. Without a prompt response from FDA, I requested information regarding the PolyHeme Study from OHRP. By letters dated March 3 and 8, 2006, I requested that OHRP provide a copy of all correspondence between OHRP and the FDA related to the PolyHeme Study, by no later than March 7, 2006, and a detailed briefing by March 10, 2006. (Attachment 1)[3]

By deadline last week, the Committee received the requested correspondence between OHRP and FDA, and for that timely response I thank the Department. After my Committee staff reviewed the materials provided by OHRP, I understand better that the FDA is not only delinquent with my requests but is equally delinquent with other offices in HHS. A review of the correspondence provided heightens my concern that the FDA did not act urgently to ensure and protect the public health. The following excerpts from emails and letters show that OHRP had a sense of urgency, anxiousness, and grave concern related to the PolyHeme Study, which OHRP officials reiterated during the briefing with my staff. In fact, as early as June 2004, OHRP raised concerns regarding the PolyHeme Study to FDA. For example, on June 28, 2004, an OHRP official contacted FDA's Director of Good Clinical Practice Programs (GCPP Director) to inform him of the following:

> OHRP has received a complaint regarding the PolyHeme trial . . . it is alleged that it is not appropriate to use the emergency informed consent waiver once subjects arrive at the hospital, because typed and crossmatched blood is available in-house after 45 min to an hour. The emergency waiver regulation requires that available treatments must be "unproven or unsatisfactory" for the waiver to be permissible, and there is concern that giving blood to trauma victims is neither "unproven or unsatisfactory." Due to the gravity of these allegations OHRP is concerned that there is an urgency for us to respond, but we wish to do so with as much information as possible. . . . We would like to meet with FDA (yourself and others in the appropriate centers) as soon as possible to discuss. (Attachment 2)

A month later, on July 19, 2004, the Director of OHRP (OHRP Director) wrote to the GCPP Director:

> Last Friday I had conversations with [FDA officials] to relay to them our sense of urgency to meet and discuss the concerns with the PolyHeme trials being discussed in the IRB community. Both agreed that we should meet ASAP. (Attachment 3)

Again the next month, on August 2, 2004, the OHRP Director contacted another FDA official:

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[3] Personal identifying information was redacted from the documents attached to this letter.

> [W]e continue to be very anxious to get together with folks from [the Center for Biologics Evaluation and Research] to talk about the PolyHeme study. Email traffic suggests an escalation of unrest within the IRB and investigator communities regarding the ethics of this protocol. (Attachment 4)

Unable to promptly and satisfactorily address concerns related to the PolyHeme Study and the Emergency Research Consent Exception through more informal communications with FDA, on November 15, 2004, the OHRP Director wrote directly to former, and then Acting Commissioner, Dr. Lester Crawford, to document OHRP's urgent concerns for the record. The Director stated that:

> [OHRP] has received . . . ethical concerns about research involving the investigational blood substitute, PolyHeme. . . . The complainants are concerned that informed consent cannot be waived under [the Waiver of Informed Consent] in the emergency room for experimental subjects to continue to receive PolyHeme, because blood is available in the emergency room and is neither "unproven or unsatisfactory." **OHRP shares these concerns.** . . . OHRP recommends that the FDA join with OHRP in conducting a review of how the FDA rule and the parallel Secretarial waiver has been implemented across the FDA and HHS. . . . Given the apparent jurisdiction of FDA in the matter of the PolyHeme complaint, OHRP is forwarding the enclosed letter to the FDA for review and, if deemed appropriate, further action.
> (emphasis added, Attachment 5)

Four months later, Dr. Crawford replied to OHRP, on March 1, 2005, and, in pertinent part, said:

> FDA staff have reviewed the issues raised in the correspondence and in additional related communications. In particular, FDA staff have reviewed the public disclosure materials submitted to the docket for the PolyHeme trial and the sponsor's sample community consultation materials, and have requested additional materials from the sponsor to help ensure the completeness of the docket. FDA staff also have discussed revisions to the community consultation materials with the sponsor for study sites where the protocol is not yet underway to more clearly describe the study. FDA will continue to take appropriate actions as needed. . . . You also mention a similar intent by the [HHS] to conduct periodic reviews for Secretarial approvals of waiver of the informed consent requirements . . . We agree that we should have further dialogue on the challenging issues raised by such research and appreciate your willingness to work with us. (Attachment 6)

On May 20, 2005, the OHRP Director wrote back:

> Thank you for your March 1 letter regarding the actions that the [FDA] has taken to address the ethical concerns . . . raised about research involving PolyHeme. OHRP also appreciates FDA's invitation to discuss the

> possibility of conducting a joint FDA-OHRP review of how the FDA emergency research informed consent exception rule, 21 CFR 50.24, and the parallel Secretarial waiver has been implemented across the FDA and HHS. OHRP would like to pursue conducting such joint review with FDA. Please let me know if FDA is willing to participate in this review, and if so, who from FDA should be our point of contact to begin these discussions. We would hope to begin this review sometime in the fall. (Attachment 7)

OHRP did not hear back from the FDA regarding this matter until seven months later when an FDA official responded to OHRP, on December 12, 2005, and, in pertinent part, said:

> This letter is in response to your previous correspondence with former FDA Commissioner, Dr. Lester Crawford, regarding the possibility of conducting a joint FDA-OHRP review of how FDA's emergency research informed consent exception rule, 21 CFR 50.24, and the Secretarial waiver at 45 CFR 46.111 have been implemented. . . . I am chairing a group which is conducting an internal review of studies submitted to the Agency under 21 CFR 50.24. We anticipate it will take some time to conduct this internal analysis, which we think is the prelude to any discussions with OHRP. . . . We agree with the sentiments of your letter that such clinical trials generate practical and ethical concerns . . . we will contact you when we have sufficiently progressed in our internal review to formulate any questions we may have that may benefit from a broader discussion. (Attachment 8)

Taken at face value, the full series of correspondence between OHRP and FDA, over the course of nearly two years, suggest a breakdown in dialogue within HHS and an apparent disregard by the FDA to zealously fulfill its mission to protect the public health. The correspondence excerpted here does not reveal the full extent of OHRP's attempts to schedule meetings with the FDA. The full correspondence also shows that FDA never fully addressed OHRP's urgent concerns regarding the PolyHeme Study or successfully scheduled a joint FDA-OHRP review of the Emergency Research Consent Exception, which according to representatives from OHRP has still not been scheduled. One might expect that the urgent concerns of OHRP would have been greeted with all due concern. Instead, the correspondence shows ineffectual attempts by OHRP to get the FDA to promptly address the ethical concerns associated with the PolyHeme Study specifically and the Emergency Research Consent Exception generally.

During the briefing last Friday, representatives from OHRP informed my Committee staff that a face-to-face meeting with the FDA took place in August 2004. However, OHRP officials confirmed that the FDA's explanations for allowing the PolyHeme Study to proceed did not satisfactorily address OHRP's concerns. In fact, my staff were told that OHRP would never have approved the PolyHeme Study.

As chairman of the Committee on Finance, I request your attention to the problems that continue to plague the FDA. In particular, I request that you intercede and expedite communication between OHRP and FDA to ensure that OHRP's urgent concerns regarding the PolyHeme Study and the Emergency Research Consent Exception

are fully addressed. A joint FDA-OHRP review of these matters should be scheduled as soon as humanly possible. Finally, I request that you see to it that the FDA provides information to the public immediately, which clearly and consistently describes the full risks, benefits, and nature of the PolyHeme study. In the meantime, my Committee staff will continue to review these matters and, undoubtedly, I will bring additional concerns regarding the FDA and the PolyHeme study to your attention. I respectfully request a response to my concerns by no later than a week from today, March 20, 2006.

Thank you in advance for your prompt attention to these critical matters.

Sincerely,

Charles E. Grassley
Chairman