ATTACHMENT ONE

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

February 23, 2006

Via Electronic Transmission

Dr. Andrew C. von Eschenbach
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

The yellow "LIVESTRONG" wristband, promoted by the Lance Armstrong Foundation, is truly a marketing phenomenon and a remarkably effective symbol on behalf of a noble cause – the battle with cancer. It was no surprise to learn that you wear one. I write today, however, because I am concerned about a far less popular and not widely worn wristband. If unsuspecting Americans were aware of the import of this light-blue wristband, it might well be a marketing phenomenon, too. It is outrageous that, for all intents and purposes, the FDA allowed a clinical trial to proceed, which makes every citizen in the United States a potential "guinea pig," without providing a practical, informative warning to the public.

As a United States Senator representing the State of Iowa and as Chairman of the Committee on Finance (Committee), which has 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. Accordingly, I have been persistent in my efforts to examine the performance of the Food and Drug Administration (FDA) in recent years. Yesterday, the *Wall Street Journal* (WSJ) ran an article entitled, "Amid Alarm Bells, A Blood Substitute Keeps Pumping," that was indeed alarming.

According to the article, the FDA is allowing a manufacturer, Northfield Laboratories, Inc., to test its product, a blood substitute called PolyHeme, in a clinical trial (the PolyHeme Study) without the consent of trauma patients, who often may be unconscious and/or otherwise incapable of providing informed consent. The PolyHeme Study is being conducted pursuant to an infrequently used FDA regulation, which allows for waiver of the informed consent typically required in clinical trials, if some sort of community outreach program is implemented, among other requirements. It is the community outreach that brings the light-blue wristbands into the mix.

For example, if you live in, next to, or travel through a state participating in the PolyHeme Study – California, Colorado, Delaware, Georgia, Illinois, Indiana, Kansas, Kentucky, Michigan, Minnesota, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Utah, and Virginia – and you suffer a traumatic injury and receive

emergency medical treatment at a participating trauma center in that state, you may, without your consent, become a human research subject for an experimental blood product (if other contingencies are also met). That is, unless you happen to be wearing a light-blue wristband imprinted with the following: "I decline the Northfield PolyHeme Study" (see attached). I suspect many people, if they knew this, might reasonably ask, "where do I get my wristband?"

It also comes as no surprise that this question is not a readily answerable one. Certainly, it's not apparent from any information on the FDA's website. Nonetheless, an unknown number of community meetings were reportedly held in the participating states. At these meetings, anyone who knew of and took time to attend a meeting could opt out of the PolyHeme Study by requesting – and wearing continuously for an undetermined period of time – one of these light-blue wristbands. However, I am skeptical that any participating medical centers managed to conduct effective, practical outreach to the community and to provide a meaningful, informative warning to the public about the PolyHeme Study. Researchers in at least one state (Oregon) suspended participation in the PolyHeme Study when it was unable to obtain local approval because the community meetings were sparsely attended. According to a news report published in the *Journal of Clinical Investigation* in July 2004, Loyola University Health System in Chicago engaged in an extensive effort to reach potential participants in specific communities. However, the turnout at meetings was "surprisingly low, averaging...between 0–5 people of those who responded." The author of this news report raised an important question: "Is this in absentia approval for the trial an inherent flaw in the initial regulation whereby people, thinking they personally are unlikely to end up in the trial, don't bother with the outreach and are therefore not truly informed?"

Despite the recent media attention associated with the PolyHeme Study, more remains unknown than known about it today. Accordingly, as Chairman of the Committee, I request that the FDA address this issue by providing the public with meaningful information related to what they should already have known about the PolyHeme Study. In addition, at the earliest opportunity, but no later than March 8, 2006, please provide my Committee with a detailed briefing regarding the PolyHeme Study. Over the next few days, my Committee staff will contact your staff with more specific requests for information, but at the minimum your staff should be prepared to address the following issues related to the PolyHeme Study:

1. What oversight, if any, has FDA conducted related to the PolyHeme Study?

2. What consultation with representatives of the community was conducted?

3. What public disclosure to communities was conducted prior to initiation of the PolyHeme Study?

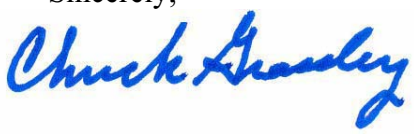
4. Were known adverse events, including but not limited to those reported in the WSJ, disclosed with the risks and expected benefits information?

5. Has Northfield Laboratories, Inc., met all regulatory reporting requirements related to its PolyHeme product, including but not limited to timely reporting of all adverse events.

Finally, I request a detailed list and summary of all clinical trials, between January 1, 1996, and the date of this request, conducted pursuant to the FDA regulation governing exception from informed consent requirements for emergency research.

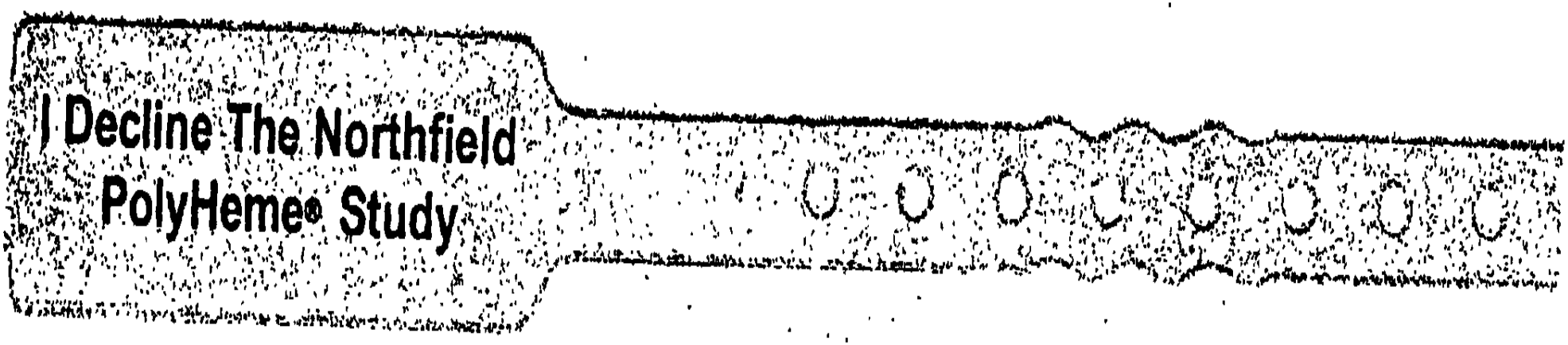
Thank you in advance for having your staff contact my Committee staff by March 1, 2006, to coordinate this briefing.

Sincerely,



Charles E. Grassley
United States Senator

Attachment


I Decline The Northfield
PolyHeme® Study

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

March 3, 2006

Via Electronic Transmission

Mr. Bernard Schwetz
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Mr. Schwetz:

As a United States Senator representing the State of Iowa and as chairman of the Committee on Finance (Committee), which has 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. Accordingly, I am concerned about an ongoing clinical trial of a blood substitute called PolyHeme (PolyHeme Study), which is manufactured by Northfield Laboratories, Inc. A number of questions have arisen about whether or not it is ethical for the PolyHeme Study to proceed without the informed consent of trauma victims who, consequently, may become a human research subject without their knowledge.

As chairman of the Committee, I request that the Office of Human Research Protections (OHRP), Department of Health and Human Services, provide the Committee with a copy of all correspondence, between OHRP and the Food and Drug Administration, that is related in any respect, directly or indirectly, to the PolyHeme Study (ClinicalTrials.gov Identifier: NCT00076648). Given the gravity of the ethical issues involved with the PolyHeme Study, I respectfully request that all correspondence be sent immediately to the Committee via facsimile, but in any event by no later than Tuesday, March 7, 2006, unless it is available sooner. If you anticipate any difficulty in complying with this deadline, please immediately contact
to make arrangements for my Committee investigators to travel to your offices to review the requested correspondence.

Thank you in advance for your prompt assistance.

Sincerely,

Charles E. Grassley
Chairman

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

March 8, 2006

Via Electronic Transmission

Mr. Bernard Schwetz
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Dear Mr. Schwetz:

Thank you for your prompt response to my request dated March 3, 2006. As chairman of the Committee, I request that the Office of Human Research Protections (OHRP), Department of Health and Human Services, provide the Committee with a detailed briefing relating to the PolyHeme Study (ClinicalTrials.gov Identifier: NCT00076648). Given the gravity of the ethical issues involved with the PolyHeme Study, I respectfully request that this briefing be scheduled before Friday, March 10, 2006. If you anticipate any difficulty in complying with this deadline, please immediately contact to make arrangements for my Committee investigators to travel to your offices to meet with OHRP staff. Please ensure that the appropriate staff are present for this briefing. My Committee staff requests the opportunity to speak with the following OHRP officials, including but not limited to

Thank you in advance for your prompt assistance.

Sincerely,

Charles E. Grassley
Chairman

(OPHS)

From: OHRP
Sent: Monday, June 28, 2004 12:24 PM
To: FDA
Cc: REDACTED
Subject: Polyheme study

Attachments: PolyHeme trial

Dear REDACTED

OHRP has received a complaint regarding the Polyheme trial (see enclosed email). In short, 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. OHRP notes that (i) this research is being conducted at several institutions that have a Federalwide assurance that applies to all research regardless of sponsorship, and (ii) continued waiver of informed consent once subjects arrive at the hospital does not appear to satisfy any permissible procedure for waiver of informed consent under HHS or other Federal regulations for the protection of human subjects. As this is an FDA-regulated product and the informed consent waiver was implemented under an FDA regulation, we need your input. We would like to meet with FDA (yourself and others in the appropriate centers) as soon as possible to discuss. Please let me know your availability over the next couple of weeks and who else at FDA you think should participate.

Let me know if you have any questions.

REDACTED
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email:

Phone:
Fax:

PolyHeme trial

ATTACHMENT THREE

(OPHS)

From: OHRP
Sent: Monday, July 19, 2004 8:48 AM
To: REDACTED (FDA)
Cc: REDACTED
Subject: Polyheme

REDACTED —last Friday I had conversations with REDACTED 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. I understand there is a conference call tomorrow to discuss Polyheme—will the right people from CBER be involved to discuss the design issues and how the FDA is going to respond to them?

(OPHS)

From: OHRP
Sent: Monday, August 02, 2004 1:41 PM
To: REDACTED (FDA)
Cc: REDACTED
Subject: PolyHeme

REDACTED—we continue to be very anxious to get together with folks from CBER 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. Also, can we please have a copy of the protocol for the PolyHeme study for our review? Thanks

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

NOV 15 2004

ATTACHMENT FIVE

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner
Food and Drug Administration
Parklawn Building, Room 14-17
Rockville, Maryland 20857

Dear Dr. Crawford:

The Office for Human Research Protections (OHRP) has received the enclosed letter raising ethical concerns about research involving the investigational blood substitute, Polyheme.

The research project referenced by the complainants appears to be subject to U.S. Food and Drug Administration (FDA) regulations for the protection of human subjects. The complainants allege that the FDA emergency research informed consent exception rule, 21 CFR 50.24, was not appropriately applied to the second part of the research study. The complainants are concerned that informed consent cannot be waived under 21 CFR 50.24 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 notes that the FDA final rule's preamble stated "The agency does intend, however, to periodically review actions on these protocols to help ensure that the rule is implemented consistently and appropriately throughout the agency." A similar intent to conduct periodic reviews was expressed by Department of Health and Human Services (HHS) when the Secretary approved a parallel waiver of the informed consent requirements of HHS regulations at 45 CFR 46.116 for certain emergency research. Given the concerns raised by the complainants, 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. OHRP looks forward to working with the FDA on such a joint review.

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.

Please do not hesitate to contact me should you have any questions.

Sincerely,

Bernard A. Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections

Enclosures

cc: REDACTED Director, CBER, FDA
REDACTED Acting Director, CDER, FDA
REDACTED Director, CDRH, FDA
REDACTED FDA
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 1, 2005

Bernard A. Schwetz, D.V.M., Ph.D.
Director, Office for Human Research Protections
1101 Wooton Parkway, Suite 200
Tower Oaks Building
Rockville, Maryland 20852

Dear Dr. Schwetz:

Thank you for your November 15, 2004, letter in which you forwarded correspondence raising concerns about research involving PolyHeme, an investigational oxygen-carrying solution. As you know from discussions between staff of the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP), we take very seriously the issues raised by the author of the correspondence and others who have commented on the clinical trial of PolyHeme.

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.

In your letter, you note FDA's commitment to periodically review actions on clinical studies conducted under the FDA emergency research regulation at 21 CFR 50.24. FDA has periodically discussed these studies and related issues within the centers and at the agency level. We have also developed a centralized process to further enhance our oversight of these studies. We also have identified the need for further review and discussion of a number of issues, including clarification of the term "unproven and unsatisfactory treatment," and clarification of responsibilities for oversight of community consultation and the expectations for such consultations.

You also mention a similar intent by the Department of Health and Human Services (DHHS) to conduct periodic reviews for Secretarial approvals of waiver of the informed consent requirements of DHHS regulations at 45 CFR 46.116. We agree that we should have further dialogue on the challenging issues raised by such research and appreciate your willingness to work with us.

Thank you for your letter and for your continued commitment to important human subject protection issues.

Sincerely,

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

MAY 20 2005

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
Parklawn Building, Room 14-17
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Crawford:

Thank you for your March 1 letter regarding the actions that the Food and Drug Administration (FDA) has taken to address the ethical concerns that the Office for Human Research Protections (OHRP) 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 a 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.

Thank you again for your willingness to work together on these challenging issues. Please do not hesitate to contact me should you have any questions.

Sincerely,

Bernard A. Schwetz, D.V.M., Ph.D.
Director
Office for Human Research Protections

cc: REDACTED FDA
REDACTED FDA
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

December 12, 2005

Bernard Schwetz, DVM, PhD
Director, Office for Human Research Protections
US Department of Health and Human Services
Tower Oaks Building, Suite 200
1101 Wootton Parkway
Rockville, MD 20857

Dear Dr. Schwetz:

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. Recently, I was asked to respond to your letter, on behalf of FDA, as 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 take seriously the FDA commitment, noted in the preamble to the final rule, to continue evaluating the implementation of 21 CFR 50.24.

We agree with the sentiments of your letter that such clinical trials generate practical and ethical concerns, and as Dr. Crawford stated in his letter from March 2005, "We agree that we should have further dialogue on the challenging issues raised by such research." To that end, 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. At that time, we may want to discuss specific mechanisms for soliciting information from the public, investigators, and sponsors about some of the issues raised.

Thank you very much. Please do not hesitate to contact me should you have any questions.

Sincerely,

REDACTED

Bioethicist, Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration
5600 Fishers Lane, Room 4B-44, HFG-2
Rockville, MD 20857

AIMS Control # 2005-3183
Cleared: 50.24 Consultative Board
CC:
50.24 Consultative Board Members

REDACTED FDA
REDACTED FDA
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REDACTED FDA
REDACTED FDA
REDACTED OHRP
REDACTED OHRP
REDACTED OHRP

Signed Hard Copy to Follow