CLINICAL TRIAL SUBJECTS: ADEQUATE FDA PROTECTIONS?

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTH CONGRESS

SECOND SESSION

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WEDNESDAY, APRIL 22, 1998

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT,
Washington, DC.

The committee met, pursuant to notice, at 1:08 p.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Cox, Horn, Davis of Virginia, Pappas, Waxman, Maloney, Barrett, Norton, Cummings, and Kucinich.

Staff present: Kevin Binger, staff director; Daniel R. Moll, deputy staff director; William Moschella, deputy counsel and parliamentarian; Judith McCoy, chief clerk; Teresa Austin, assistant clerk/calendar clerk; Laurie Taylor, professional staff member; Will Dwyer, director of communications; Ashley Williams, deputy director of communications; Robin Butler, office manager; Cherri Branson, minority counsel; and Ellen Rayner, minority chief clerk.

Mr. BURTON. The committee will come to order. A quorum being present, the Committee on Government Reform and Oversight will start its business.

I ask unanimous consent that all Members and witnesses' written opening statements be included in the record and, without objection, so ordered.

Today is the third in a series of hearings examining issues relating to the Food and Drug Administration and its policies affecting American citizens in need of medical care. We began this series in February, addressing ways to expand access to alternative and investigational therapies. We heard from patients and experts who testified about the need for change, both in the way the FDA allows treatment through compassionate use of investigational drugs as well as the need for legislation that would give all Americans the freedom to choose their own medicine.

Today, we hope to hear from the Lead Deputy Commissioner from FDA, Michael Friedman, on those issues and to introduce another issue of concern in patient care. That is, the withholding of therapeutic care from patients who are enrolled in high-risk clinical trials, many of which are approved and regulated by the Food and Drug Administration.

The FDA has prided itself on its regulatory process of drug approval as one which fully protects Americans from unsafe products. But it is troubling to learn that the agency continues to approve the use of Americans who are at high risk for serious illness and

death in its clinical trial process in ways that are considered by many research scientists to be completely unethical. Specifically, I am talking about the exposure of clinical trial subjects to periods of, quote, washout, end quote, where they are taken off medications which are significantly improving their condition and longevity. Another common method of testing new drugs is the study of a group of patients who are given a placebo, once again taken off of their current medications, and switching them to a treatment that has no therapeutic value. These procedures are undertaken daily throughout our country in the name of scientific advancement.

But what happens to those who are at high risk of danger, and who submit themselves to such experiments without understanding the dangers involved?

The FDA may say that clinical trial subjects are required to give their consent to such experiments after being fully informed of the risks involved. But do patients with severe depression, attention deficit disorders, or even schizophrenia have the ability to fully understand what they are agreeing to?

We will hear today from a renowned research scientist, Dr. Adil Shamoo, who has found through his own studies that they do not. What's more, he has found that when subjects are lost through adverse reactions or suicide during the washout and placebo phases of research, these casualties are almost never reported to the Food and Drug Administration. How can we better insure that these patients are not being treated improperly or used as guinea pigs?

And what about patients who have potentially deadly illnesses, for which there is an existing treatment? Should we ever, in the name of science, take them off of all therapeutic treatment, placing them at risk for death or serious illness? There is a growing chorus of research scientists throughout the world who say that such a practice is unethical and unacceptable. Yet, the FDA continues to promote the use of placebos in research where patients are at high risk of severe danger or even death.

We will hear today from Joe Foster, a man whose life was changed forever when he was taken off of the medication his doctor had prescribed to control his blood pressure. He entered a clinical trial and was told by the new doctor that his health would be closely monitored. He was then sent home with a bottle full of sugar pills. He suffered a heart attack and a stroke within several days.

This clinical trial was designed to test a new drug against a placebo, and Joe Foster will tell you that if he had understood what could happen to him, that he would not have volunteered for that trial.

Today, we will also hear from Dr. Peter Lurie, a highly esteemed doctor of research methodology. He will explain why FDA should discontinue its promotion and approval of trials that place a controlled group of patients at such a high risk of harm.

At our previous hearings, we heard testimony about the need to promote the progress of medicine and that further testing of alternative therapies is needed. But it needs to be accomplished in rational ways, using methods that do not endanger the subjects. As I have stated in the past, not many dying cancer patients want to part of a test where they will end up with a placebo and no chance for survival. And, indeed, in the field of cancer research, placebo

trials are almost unheard of. So why does FDA continue to require their use in other areas of research?

Medical progress is important to our future. But the process of scientific proof should not take us backward in history. The 40-year Tuskegee study in which treatment was withheld from black men with syphilis and the injection of live cancer cells into elderly patients in the 1960's should serve as a stark historical reminder of the abuses that can occur in the name of science. However, this past week in New York City it was revealed that the New York Psychiatric Institute conducted experiments on young boys and girls by injecting them with fenfluramine, a substance first approved by the FDA and later banned because of potentially deadly side effects. This drug was found to cause heart valve damage in adults and, as yet, there is not enough evidence to show that it does not hurt children. What's more, this drug was injected into children to study its effects on their brains, not because it would benefit them in any way.

Yesterday's paper reported that the experiments on children continued even after the drug was banned by the FDA, with an FDA spokesman stating that this experiment using inner-city children was apparently grandfathered in. If the drug was banned for use in adults, certainly the FDA should have banned its use in children.

This is startling news in modern-day America and provides further evidence that somewhere the system has broken down. What are the rights of experimental subjects, especially children who may be subjected to a treatment that could harm them? What safeguards are afforded after a drug is banned in the marketplace, to ensure that these experiments do not continue? Perhaps Dr. Friedman from the FDA, who is highly credentialed in research and medicine, will be able to shed some light on this matter.

We have an obligation to answer these questions, to encourage the practice of medicine which focuses on the best interests of the patients, rather than sacrificing the rights, health, and safety of the patients to accomplish the objectives of science.

I would like to welcome all of our witnesses here today and look forward to hearing their testimony. I would ask that all witnesses summarize their testimony in 5 minutes. Your full statements will be submitted for the record. And with that, I now recognize my colleague, Mr. Waxman, for his opening comments.

Mr. WAXMAN. Mr. Chairman, the protection of human research subjects has a history replete with disturbing abuses and great successes. Although the horrors of Tuskegee and Willowbrook are fresh in modern memory, the principle of informed consent and our country's "common rule" of human subject protections have served as the foundation for successes in biomedical research and medical innovation.

There's no question that our system of human subject protections could be stronger. Institutional Review Boards or IRBs should be registered with the Federal Government. Privately sponsored research in some settings currently evades Federal oversight and the common rule of Federal protections should apply to all research in this country, but does not.

These are legitimate issues which deserve further exploration. Last year, this committee took its initial steps through a thoughtful and comprehensive subcommittee hearing chaired by Congressman Shays. Testimony was given by all of the key Federal officials, including the Director of NIH, Dr. Harold Varmus; Surgeon General David Satcher, then Director of CDC, the Centers for Disease Control; Food and Drug Administration Deputy Commissioner Mary Pendergast; and the Secretary's Science Adviser, Dr. William Raub.

This afternoon, we will go over some of that same ground. One of today's witnesses testified at that earlier hearing, and I hope we will have as constructive an afternoon as was spent last year in Mr. Shays's subcommittee.

These issues are tough issues. To compare the use of a placebo in a clinical trial with anything like the Tuskegee horrors I believe is off-base. The only way to get a clear understanding of the science is to use a placebo. But there is a tension. There is a tension in using a placebo when we have an alternative therapy where you have a treatment. And, under those circumstances, serious ethical questions are raised. We are looking at the edges of science, the places where science is pushing forward and pushing against ethical considerations.

These are tough calls. The first calls are those made by the scientists themselves. They are dealing with uncertainties. They are, however, on the first line. Later FDA is involved. It's easy to blame, but is not particularly constructive to do so. These are tough and complex issues, and it is a challenge for everyone involved to make the right decision.

Finally, I want to note for the record my concern over the last-minute problems with this hearing's organization. Until a few days ago, it was the committee's commitment and stated intention to convene another hearing relating to patient access to unapproved therapies. Only on Friday did the administration and the Democrats learn that informed consent and human subject protections would be the subject of the hearing. In other words, the subject of this hearing was changed Friday without any notice to anybody. Not that this is not an important hearing, not that this is not a worthwhile hearing to have, but people ought to be given advance notice of it. Only yesterday, after objections were raised, was the administration finally granted its traditional privilege of testifying first, and only this morning was certain testimony provided to the FDA, by which I suppose they're supposed to comment. I trust in the future that such irregularities will be avoided and a regular order will be observed. Without objection, I wish to submit with my statement a letter from the minority staff to the chairman regarding these irregularities.

Without further delay, Mr. Chairman, I want to yield back the balance of my time. I look forward to the testimony of the witnesses. I have one request to make—and I apologize to all the witnesses—that I have a conflict in my schedule and won't be here to

hear them and to ask questions. I'd ask unanimous consent that the record be held open so that all the witnesses that appear will have an opportunity to respond to questions in writing that may be submitted to them by me and any other member of the committee.

[The prepared statement of Hon. Henry A. Waxman follows:]

STATEMENT OF CONGRESSMAN HENRY A. WAXMAN
GOVERNMENT REFORM AND OVERSIGHT COMMITTEE
HEARING ON
"FDA VIGILANCE IN PROTECTING
HUMAN SUBJECTS OF CLINICAL TRIALS"
WEDNESDAY, APRIL 22, 1998

Mr. Chairman, the protection of human research subjects has a history replete with disturbing abuses and great successes. Although the horrors of Tuskeegee and Willowbrook are fresh in modern memory, the principle of informed consent and our country's "Common Rule" of human subject protections have served as the foundation for successes in biomedical research and medical innovation.

There is no question that our system of human subject protections could be stronger. Institutional Review Boards (IRBs) should be registered with the Federal government. Privately sponsored research in some settings currently evades Federal oversight. And the "Common Rule" of federal protections should apply to all research in this country, but does not.

These are legitimate issues which deserve further exploration. Last year, this Committee took its initial steps through a thoughtful and comprehensive subcommittee hearing chaired by Mr. Shays. Testimony was given by all of the key federal officials, including the Director of NIH, Dr. Harold Varmus; Surgeon General David Satcher, then director of CDC; FDA Deputy Commissioner Mary Pendergast; and the Secretary's Science Advisor, Dr. William Raub.

This afternoon, we will go over some of the same ground. One of today's witnesses testified at the earlier hearing. I hope we will have as constructive an afternoon as was spent last year in Mr. Shay's subcommittee.

Finally, I want to note for the record my concern over the last minute problems with the hearing's organization. Until a few days ago, it was the Committee's commitment and stated intention to convene another hearing "relating to patient access to unapproved therapies." Only on Friday did the Administration and Minority staff learn that informed consent and human subject protections would be the subject of this hearing.

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I trust in the future that such irregularities will be avoided and the regular order observed. Without objection, I wish to submit with my statement a letter from the Minority staff to the Chairman regarding these irregularities.

Without further delay, I welcome the witnesses and look forward to their testimony.

DAN BURTON, INDIANA
CHAIRMAN

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ONE HUNDRED FIFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

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HENRY A. WAXMAN, CALIFORNIA
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INDEPENDENT

April 21, 1998

The Honorable Dan Burton
Chairman
Committee on Government Reform and Oversight
2157 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Chairman:

The purpose of this letter is to express my concern about the subject matter and scope of the hearing entitled "Clinical Trial Subjects: Adequate FDA Protections?," which is scheduled to convene on April 22, 1998.

As you may recall, I wrote to you prior to the February 4, 1998, hearing on "Patient Access to Alternative Treatments: Beyond the FDA." In a letter dated January 30, 1998, I requested that the FDA be asked to testify before the Committee on February 4, to allow members to raise any questions or issues which may havve arisen from testimony of the invited patients. You denied that request, but your staff assured the minority that the FDA would testify and have an opportunity to respond to issues raised at the February 4 hearing at a later date.

This issue also arose at the February 12 hearing. During this hearing, you said "we're going to be having the FDA before this committee on a regular occasion until we get some answers" (p. 35); and "our pursuit of the FDA in trying to bring about fairness will continue and will be resolute" (p.35). On several occasions, you asked witnesses for questions or recommendations to present to the FDA (p. 68; p. 78).

Unfortunately, it now appears that you are not following this commitment. Although FDA has been invited to attend the hearing on April 22, the subject matter is substantially different than patient access to alternative treatments. According to the hearing notice and the majority briefing memorandum, the focus of the hearing will be patient protections in controlled trials. This does not afford FDA a chance to respond to allegations raised at previous hearings.

Serious charges were made at the February 4 hearing. During the hearing, you asserted

"the FDA often gets in the way of our choices of alternative medicines and treatments" (p. 3); "the FDA dictates what treatments doctors can use in treating serious illnesses, but most of those are toxic and often dangerous to already-weakened patients" (p. 6); "the FDA has harbored a culture of intimidation and sometimes harassment against those who are looking for alternative cures" (p. 6); "the FDA process is broken" (p.8); and "the FDA shuts off every avenue to people-and we've had some witnesses here today who have had those avenues shut-off -- it's pretty inhumane" (p. 139). Because of the serious nature of those statements, the agency must have a chance to respond. Failure to provide that opportunity is unfair and damages the credibility and impartiality of this investigation.

I am also troubled by the inadequate notice provided to the agency. In a letter dated April 8, 1998, the FDA is invited to appear before this committee to "offer testimony relating to the Food and Drug Administration and its regulations pertaining to clinical trials and patient access to unapproved therapies." However, according to the hearing notice and the majority's briefing memorandum distributed on April 17, 1998, witnesses at the upcoming hearing are expected to provide testimony about "the FDA's oversight and protection of clinical trial subjects." There is a major variance between issues involving access to unapproved treatments and questions involving patient protections in clinical drug trials. Access involves examination of the process and procedures used by the FDA and manufacturers in establishing and conducting drug trials. However, issues involving patient protections involve assuring the safety of patients who are participating in clinical trials. While these issue are both related to FDA's oversight responsibilities, they involve significantly different aspects of the agency's function and therefore raise different public policy concerns.

This major change in the focus and direction of the hearing is not an insignificant matter. If the agency's testimony conforms to the letter it received from the Committee, it will not be responsive to issues raised in the hearing notice and majority's briefing memorandum. This is unfair to the members of the Committee. Because the agency has not been informed about this change in direction, it cannot respond to issues raised in the memo. Members will be deprived of the opportunity to raise questions and receive meaningful answers about the topic as presented in the memorandum.

Additionally, this major change in hearing scope effectively precludes the FDA from responding to concerns raised by witnesses at previous hearings.

Finally, custom and practice of this institution provide that absent exigent circumstances, witnesses representing Executive Branch agencies appear on the first panel at any hearing. I urge you to follow this procedure.

Sincerely,

Henry Waxman
Ranking Minority Member
Committee on Government Reform and Oversight

cc: The Honorable Michael A. Friedman
Acting Commissioner
Food and Drug Administration

Mr. BURTON. Without objection, your additional correspondence will be put in the record and we will also add, without objection, the response to that. Now does any other Member have a——

Mr. WAXMAN. Mr. Chairman, I ask also unanimous consent to submit questions in writing.

Mr. BURTON. Without objection. Do any other Members have an opening statement?

[No response.]

Mr. BURTON. If not, we'll ask Dr. Friedman to stand. Please raise your right hand——

Dr. FRIEDMAN. Sir, would—those others who are accompanying me who might wish to respond to questions, would you like them also to be sworn in at this time, sir?

Mr. BURTON. Sure. That would be fine. That would be a good idea to have them sworn as well in case they have to give testimony.

Dr. FRIEDMAN. Please, if you would.

Mr. BURTON. Did you bring your whole staff with you?

Dr. FRIEDMAN. Given the importance of the hearing——

Mr. BURTON. That's fine. That's fine.

[Witnesses sworn.]

Mr. BURTON. Be seated.

Dr. FRIEDMAN. Thank you.

Mr. BURTON. You have an opening statement, Dr. Friedman?

STATEMENT OF MICHAEL FRIEDMAN, M.D., LEAD DEPUTY COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DIANE MALONEY; ROBERT TEMPLE; STUART NIGHTINGALE; DIANE E. THOMPSON; ROBERT DELAP; PATRICIA KEEGAN; AND PATRICIA DELANEY

Dr. FRIEDMAN. Yes, sir, if I may. Mr. Chairman and committee members, I'm here today serving as the Acting Commissioner for the Food and Drug Administration, and I'm pleased to be here to help you with your inquiries and with this discussion on what until a couple of days ago I understood the subject of this hearing, the various programs that we have at FDA for providing access to promising therapies for seriously ill and dying patients. Now other members of the agency are here with me to respond to questions, since I do recognize that there are other areas that you would like us to try and address, and we will do our best to do so.

But let me reaffirm, if I may, that our commitment to programs which provide access is intensive, is longstanding, and it's unequivocal. And I speak to this important issue today with no arrogance nor with any self-righteous egotism, but with a profound compassion and a desire to see how we can further improve our systems because we are committed to doing so.

Fundamentally, we believe this to be an issue of balance. On the one hand, we want to optimize the opportunities for today's patients, with serious and life-threatening diseases who sometimes lack truly satisfactory treatment options to have access to promising experimental interventions, interventions that have yet to be proven safe or effective. At the same time, we want to make sure that all future patients with that disease are afforded the best therapies. Hence, we continue to have sponsors developing new

treatments, performing studies needed to show that these treatments are actually safe and actually effective for a defined group of patients.

Many products appear to be promising in early stages of development only to prove ineffective or in fact even detrimental upon closer scrutiny. It's been estimated that perhaps 80 percent of all drugs that undergo testing in humans are abandoned early in research because they proved to be unsafe or ineffective or otherwise unsatisfactory. Unless careful, well-designed studies are performed and analyzed, countless future patients will be needlessly harmed by dangerous or useless interventions.

Historically, FDA was created because of injuries and deaths caused by carelessly made or poorly tested pharmaceuticals, starting early in this century. With each disaster, Congress added to FDA's responsibilities for ensuring that products are safe and effective. Our capacity to promote and to protect the health of the consumer rests on rational, science-based and safety decisions about the medical products offered in the United States. Access to products is terribly important. But I suggest that even more important is the information associated with those products to allow them to be used properly. Information about how best to employ treatment, that's what's fundamentally important.

The best way to gain this information is through formal clinical trials in which new therapies are tested in volunteers. The conditions of this testing must be carefully controlled, carefully scrutinized and must be of the highest ethical principles. There are appropriate procedures for conducting clinical trials. Now these clinical trials are often complicated, they take time to complete the approval phase, to have sufficient followup, to be interpreted and reported and analyzed and I certainly sympathize with the frustration and the sense of urgency that Congress, the sick individuals, and their families and friends have as they wait for clinical studies to provide answers.

As a physician who has cared for cancer patients myself, I have felt this same frustration. As a family member, as a colleague, I have experienced these same emotions. I know what it is to watch the best available treatments fail to stop the disease. I know firsthand what it's like to see desperation and anger rise up in patients or in family members as time appears to be running out when available treatments fail to benefit. There is a frantic search for the next experimental treatment that holds the promise of lengthening life, expanding time or comfort, and, yes, even providing a miracle.

At this stage, patients and their families don't want to hear about scientific process or overall public health goals of providing safe and effective therapies for all patients. They want to try anything and they want it now. They object to any institution that they perceive standing between them and a treatment they believe may help. I do understand that. I also know that this is the time when patients and their families are most vulnerable to the seduction of promised miracle cures that work like mirages just beyond the borders of medicine.

As a physician, serving as the Acting Commissioner, it's my job to help patients and those that care about them and for them to find the most effective therapies and to get access to accurate infor-

mation to allow for informed choices. It's FDA's job, written into the law by Congress and reaffirmed as recently as last year, to protect patients from untested and unproven products and to promote the public health with good options. The best way to do that remains with controlled clinical trials which provide the foundation for evidence-based medicine. And I understand that there will be questions probably later about the exact structure of those trials and I look forward to trying to provide some answers to you.

There's promise here. Clinical studies are a very active part of medical research. More than 13,000 active drug and biologic studies are currently filed with FDA. As many as 50,000 patients may be enrolled in a single study and it's estimated that more than 120,000 patients are enrolled for a year just in NIH-sponsored clinical studies.

Clinical trials have taught us many important lessons about the safety and effectiveness of whole classes of products. They've also shown how our notions and beliefs about a drug can be simplistic, naive, and, in some cases, even dangerous. I'll give you one example, if I may. A drug clarithromycin is an antibiotic used to treat atypical mycobacterium infections, simply referred to as MAC. It's an infection related to tuberculosis. It tends to strike people with damaged immune systems. It's one of the fatal complications of AIDS. In the laboratory, clarithromycin was highly active against this microorganism.

Because the drug was already on the market, physicians started using it in high doses to treat patients with MAC before clinical trials were completed. It was a sensible approach; it was a thoughtful approach; and such high doses have been the best way of reducing the severity of the infection in the past. In this case, however, two early studies showed unexpectedly an increased death rate in the high-dose group. This was completely unexpected. It was rather counterintuitive. The patients receiving the high dose had better control of their infections. They should have lived longer than with the low-dose group. They did not. A third study confirmed this finding, including the fact that a lower dose actually extended life. Now if the clinical studies had not been performed, doctors might still be using the wrong dose with fatal results.

While I believe in the power and the utility of clinical trials, I do not want FDA to construct administrative barriers that delay effective treatments needed by sick patients. FDA is committed to providing early access to promising but unproven interventions for seriously ill patients who might otherwise have no hope. There are many examples I can give. Nifedipine is one particular example, but there are many others.

To give patients a place to get information they need, FDA established the Office of Special Health Issues. Most callers want information about treatments currently being researched. These calls by their nature are difficult and sensitive ones. This staff is trained to provide as much assistance as possible to patients, to family members, and others undergoing extremely difficult times and to help them with—research their treatment options.

Mr. Chairman, I know the time for this statement is short. I want to say just a word if I may about alternative therapies. Let me assure you that FDA does not care where a new product comes

from—a flower growing in the Amazon, a biotech laboratory, anywhere. What does matter is that a product is manufactured consistently and with high quality; studied scientifically in properly controlled clinical trials so we can know whether it's safe and works for a specific purpose; and that the persons who participate in those clinical trials are adequately protected, fully informed of the risks and possible benefits of their participation.

Before I close, I'd like to say just a word about the proposed piece of legislation, the Access to Medical Treatment Act, H.R. 746. We believe this legislation, while well-intentioned, would unfortunately lower the standards for safety, thus putting patients at unnecessary risk. We also believe this legislation would have at least three unintended consequences. First, by allowing access to unapproved therapies outside of the investigational new drug, biologic, and device processes, the bill would reduce or eliminate the critical process of scientific data collection necessary to establish the safety and effectiveness of the product. Second, assurance of appropriate informed consent, the issues that you brought up so cogently, in human subject protection we believe would be diminished. And, third, the bill would make it very difficult to protect consumers against health fraud.

We've learned a great deal about expanded access and expedited product approval from the various programs we've implemented to provide access to unapproved products. We have learned that uncontrolled expanded access cannot coexist with the need to pursue controlled clinical trials which provide the information necessary to serve everyone's interests. We need to work under controlled situations. We also understand the need for speed. We need—in recent years we've really revitalized our product approval and review processes. It has been our goal to improve access to promising therapeutic agents without compromising the thoroughness and integrity of the scientific review, the development or the rights of the individual patient participating. We really work to make sure that human subjects do receive the protection they deserve.

[The prepared statement of Dr. Friedman follows:]

Mr. Chairman, Members of the Committee, I am Michael A. Friedman, M.D., Lead Deputy Commissioner for the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the various programs for providing access to promising therapies for seriously ill and dying patients. Our commitment to these programs is longstanding and unequivocal. While most of our attention today will focus on drugs and biologics, my written statement also covers medical devices to provide the Committee information on the full scope of FDA's activities and of H.R. 746, "The Access to Medical Treatment Act."

Under the Federal Food, Drug, and Cosmetic (FDC) Act and related statutes, the Government has a vitally important role in helping to ensure that the medical products upon which patients and their health care practitioners rely are both safe and effective. These safeguards are particularly important for our most vulnerable citizens, those who are desperately ill. We believe the existing programs under which patients can obtain access to experimental therapies, and those under which we expedite approval of such therapies, establish the appropriate framework for achieving our mutual goal of providing patients with serious and life-threatening diseases the earliest reasonable access to promising therapies. These programs were codified in the recently enacted "Food and Drug Administration Modernization Act of 1997" (FDAMA). Of course,

we recognize the value of even more effective access programs, and as we proceed with implementation of FDAMA, we will focus particularly on ways to improve the effectiveness of these processes.

Finally, as I discuss below, we have significant concerns with H.R. 746, "The Access to Medical Treatment Act." This legislation would lower the standard for safety, thus putting patients at unnecessary risk. We also believe this legislation would have at least three unintended consequences. First, by allowing access to unapproved therapies outside of the investigational new drug, biologic, and device processes, the bill would reduce, or eliminate, the critical process of scientific data collection necessary to establish the safety and effectiveness of a product. Second, assurance of appropriate informed consent and human subject protection would be diminished. Third, the bill would make it very difficult to protect consumers against health fraud.

I. THE STATUTORY AND REGULATORY FRAMEWORK

FDA's primary mission for over 90 years has been to promote and protect the public health, as directed by the FDC and Public Health Service Acts. These statutes were enacted and amended, in part, in response to devastating public health tragedies resulting from the sale to, and use by, an unsuspecting public

of unsafe and ineffective products sold as medicines and medical devices. The FDC Act requires that new drugs be shown to be safe and effective before being marketed in this country.

The requirement that a person wishing to sell to the public a product to prevent, cure or mitigate illness or injury must first prove that such product is safe, and actually does what the vendor claims it does, is the single most important consumer protection provision of these statutes. It is this statutory provision that affords consumers the most effective protection against untested and unproven products. Sadly, such products most often are promoted to desperate victims of illness and injury.

A new drug or biologic (referred to in this statement as "drug") may not be distributed in interstate commerce (except for clinical studies) until a sponsor, usually the drug manufacturer, has submitted and FDA has approved a New Drug Application (NDA) or a Biologics License Application (BLA) for the product. For approval, an NDA or BLA must contain sufficient scientific evidence demonstrating the safety and effectiveness of the drug for its intended uses.

The evidence of safety and effectiveness usually is obtained through the conduct of controlled clinical trials. The disciplined, systematic, scientific conduct of such trials is

the most effective and efficient means of getting the data which will let the patient/consumer and his or her health care practitioner know how to use the new product so that it will have the most beneficial effect.

A. INVESTIGATIONAL NEW DRUG APPLICATION PROCESS

To obtain approval for a new drug, the first step a sponsor usually must take is to test the drug in animals for toxicity. The sponsor then takes that animal testing data, along with additional information about the drug's composition and manufacturing, and develops a plan for testing the drug in humans. The testing plan generally is referred to as the protocol. The sponsor submits these data, along with its study plan, the qualifications of the investigators who will conduct the clinical studies, and assurances of informed consent and protection of the rights and safety of the human subjects, to FDA in the form of an Investigational New Drug application (IND).

FDA reviews the IND for assurance that the proposed studies, generally referred to as clinical trials, do not suggest that human subjects might be exposed to unreasonable risk of harm. FDA also verifies that there are adequate assurances of informed consent and human subject protection. At that point, the first of three phases of study in humans can begin.

Phase 1 studies primarily focus on the safety studies of the drug in humans. Phase 1 studies carefully assess how to safely administer and dose the drug with an emphasis on evaluation of the toxic manifestations of the therapy, how the body distributes and degrades the drug, and how side effects relate to dose. Phase 1 studies typically include fewer than 100 healthy volunteers or patients.

The next step, called Phase 2 studies, are clinical studies to evaluate the effectiveness of the drug for a particular indication and to determine common short-term side effects. Phase 2 studies typically involve a few hundred patients. Importantly, it is estimated that 80 percent of all drugs tested are abandoned by their sponsors after either Phase 1 or 2.

Once Phase 2 studies are successfully completed, the drug's sponsor has learned much about the drug's safety and effectiveness. At this point Phase 3 studies, involving up to several thousand patients, may be conducted. These studies can examine additional uses, obtain further safety data including long-term experience, and consider additional population subsets, dose response, etc. FDA strongly encourages sponsors to work closely with the Agency in planning definitive Phase 3 clinical trials so as to help assure that the trials are

designed to have the greatest likelihood of producing results sufficient to permit product marketing.

Once Phase 3 trials are completed, the sponsor submits the results to FDA in the form of an NDA. FDA's medical officers, chemists, statisticians, and pharmacologists review the application to determine if the sponsor's data in fact show that the drug is both safe and effective. The manufacturing facility is evaluated to confirm that the product can be produced consistently with high quality. Of note, it is common to allow participants in Phase 2 and 3 studies to continue on a therapy if it seems to be providing benefit. This practice provides longer term safety information at an early stage in this process.

At present, there are literally thousands of clinical trials ongoing, involving hundreds of thousands of patients. There are over 13,000 active drug and biologic INDs filed with the Agency, with as many as 50,000 patients enrolled under a single IND. It is estimated that well over 100,000 patients are enrolled per year in NIH sponsored treatment clinical trials alone. In addition, there are hundreds of clinical trials assessing approved drugs for new, unapproved uses that are conducted under the auspices of local Institutional Review Boards.

Results of controlled clinical trials are the basis of evidence-based medicine. They allow physicians and patients to utilize therapies with a clear understanding of their benefits and risks and, in some cases, a basis for strong public health recommendations for treatments. Clinical trials also have saved us from disastrous public health consequences as illustrated below.

For example, when AZT was the only approved AIDS treatment, ddC was made available under treatment-IND for the several years while clinical trials were underway. These trials were to assess whether ddC was superior to AZT or if it was effective for patients intolerant of AZT. Although the product could cause permanent, sometimes severe nerve damage, there was great demand for early access to the product. It was even manufactured by sources other than the company (probably by amateur chemists) and this "bath-tub" ddC was made available through buyers clubs when the demand exceeded the sponsor's supply. FDA acted with the sponsor, the buyers clubs, patient advocates, and investigators to make more of the drug available and get the illicit, poorly manufactured product off the market.

What did the ddC clinical trials show? In a head-to-head comparison versus AZT as initial therapy, an independent data safety monitoring board stopped the trial early because the

death rate in the ddC group was at least twice higher than in the AZT group. For patients intolerant to AZT, a clinical trial compared switching to ddC versus ddI. In this study the trend was that ddC had superior survival to ddI. Later studies showed that ddC in combination with AZT had superior survival to AZT alone. Each of these studies involved hundreds of patients and was essential to determining where ddC improved survival and where it did not. Although some of the early access uses were later found to be poor choices, it was considered reasonable at the time to provide the drug while the question was still being answered. The important point is that patients are only well served by early access when the controlled clinical trials proceed in parallel with early access.

A second example that illustrates the need to conduct trials is Clarithromycin for treatment of atypical mycobacterial infections (Mycobacterium-avium-intracellulare complex or MAC). This infection, related to tuberculosis, is an infection of patients with damaged immune systems and is one of the fatal complications of HIV infection and AIDS. In cultures of the MAC organism, clarithromycin is one of the most active drugs against the organism. Before clinical trials were completed, it was used widely in high doses to treat MAC. Such doses have the best effect on reducing the severity of the infection. In this case, the early access trials randomized patients to high

and low doses as did the controlled clinical trials. Both trials demonstrated an increase in the death rate in the high dose group, even though there was better control of MAC.

This was a totally unexpected, counter-intuitive result. A third trial was done which showed the same higher death rate in the high dose group. Had the product simply been used off-label (it had other approved uses) clinicians using MAC control as their rationale for treatment with high doses might not have recognized the fatal toxicity of chronic high doses of the drug. At the lower dose this drug was life-extending.

At the same time, it cannot be disputed that as science and technology have advanced, proving that a product is safe and effective can require considerable effort, time, and money. This makes our system of drug development particularly susceptible to market forces. Most new therapies today reach the market because a private commercial entity was willing to invest in the development and testing process necessary to bring a product to the market.

I want to stress that it does not matter to FDA whether a product is characterized as "mainstream" or "alternative"; it does not matter whether the product was synthesized in a state-of-the-art laboratory or was found in the Brazilian rain forest. What does matter is that a product is manufactured

consistently and with high quality; studied scientifically in properly controlled clinical trials, so that we can know whether it is safe and works for a specific purpose; and that the persons who participate in clinical trials are adequately protected and fully informed of the risks and possible benefits of their participation. The Agency frequently works with sponsors and investigators, whether in large organizations or as individuals, to facilitate the development of new products. The amount and kind of information that is required for any new product is commensurate with the risks involved and the complexity of the issues that the particular product presents.

There are many examples of products used in complementary and alternative medical practice that are being evaluated either in the United States or abroad, under an IND, including the following:

St. John's Wort (Hypericum) for depression;

Ginkgo biloba for cognitive impairment/cerebrovascular insufficiency vascular indications;

Chinese Herbal product mixture for postmenopausal hot flashes;

Chinese Herbal preparation (topical) for plantar warts;

Chinese Herbal preparation for HIV-associated chronic synositis;

Saw Palmeto for benign prostatic hypertrophy;

Green Tea extract(s) for cancer;

Shark cartilage extract for advanced lung and other cancers;

Ozone therapy for transfusion-related diseases;

Melatonin for chronobiology and reproductive indications;

Antineoplastons for cancer;

Dietary Arginine Supplements for cancer;

Vitamin D for cancer; and,

Zinc Supplementation in Head and Neck cancer patients.

B. EXPEDITING APPROVALS AND EXPANDING ACCESS TO INVESTIGATIONAL PRODUCTS

Let me emphasize that FDA is committed to providing early access to promising, but unproven, medical treatments for seriously ill patients who might otherwise have no hope. The Agency for many years has worked to provide patients broad access to unapproved therapies. For example, Nifedipine, first approved in 1981 under the brand name Procardia, was the first calcium channel blocker. Prior to approval, tens of thousands (20,000 to 30,000) of patients had access to the drug in open protocols. In recent years, FDA has reexamined the product approval and review processes to identify ways to improve access to promising therapeutic agents, without compromising the thoroughness and scientific integrity of their development or of the review of such products, or the protection afforded to human subjects. Importantly, we also are addressing ways to improve public awareness of these processes.

Our efforts are aimed at two main areas: 1) to speed the approval process of important new drugs, biologics, and medical devices, including expedited review, priority review, and accelerated approval; and 2) to expand the availability of promising, but unapproved, products to seriously ill patients. FDA has developed regulations and issued guidance documents that explain when a breakthrough product can be approved before clinical research is completed (accelerated approval). These documents also describe how and when promising, but unapproved, therapies can be made available to patients while controlled trials are still in progress (e.g., treatment IND and parallel track). These efforts reflect an evolving institutional philosophy supportive of more thoughtful risk-taking in the pursuit of safe and effective products with describable benefits and toxicities for patients with serious and life-threatening diseases that are not well-treated by available therapies.

We still believe that the best means of providing access to useful medical treatments for all Americans is to continue to shorten the review and approval times and to continue to work with industry to shorten development times for drugs, biologics, and medical devices. Today, we are approving drugs in time periods that are as fast, or faster, than any country in the world with a comparable system of human subject

protection. We are doing so while maintaining our longstanding standards for safety and effectiveness.

In addition to our overall efforts, we have implemented a number of specific initiatives targeted at products for serious and life-threatening diseases. These include the expedited review procedures (21 CFR Part 312, Subpart E), the accelerated approval process for certain drugs and biologics (21 CFR Part 314, Subpart H and 21 CFR part 601, Subpart E), and our commitment to early and frequent meetings with product sponsors, among other efforts. All of these efforts have contributed substantially to shortening the time for many important products to get to market.

Despite this important progress in speeding therapies to market, FDA recognizes that, for a person with a serious or life- threatening disease, who lacks a satisfactory therapy, a promising but not yet fully evaluated product may represent the best available choice. FDA wants such patients to have early access to promising medical interventions. FDA has worked hard to balance two compelling factors: the need for the disciplined study necessary to identify treatments that may improve patients' health; and, the desire of seriously ill persons, with no effective options available, to have the earliest access to unapproved products that could be the best therapy for them. The specific programs FDA has put in place

to expedite the approval of promising investigational drugs and medical devices and to make them available to the very ill as early in the development process as possible without unduly jeopardizing their safety, are described in detail in the Appendix.

Importantly, these issues were considered extensively during Congressional action in 1996 and 1997 on FDA reform and modernization legislation. Congress affirmed the approach the Agency has taken by codifying in FDAMA the expanded access and expedited approval programs developed by the Agency. Congress specifically included the safeguards the Agency had incorporated into those programs. As guided by FDAMA, FDA currently is reviewing its processes to optimize the Agency's ability to assist and expedite development of, and access to, important new products for serious and life-threatening illnesses.

C. ROLE OF SPONSORS, INVESTIGATORS AND PATIENTS IN IND PROCESS

It should be noted that in the drug development process, FDA's primary point of contact is with the sponsor of the product, or sometimes with a patient's physician, who is seeking permission to use an investigational therapy on an individual patient. This is true even in the case of an individual patient who is

seeking access to an investigational therapy for herself, and may or may not be eligible for enrollment in a clinical trial. The sponsor of the investigation must decide whether it is willing to make the product available to the patient. Assuming it is, and such access cannot be provided through an existing protocol, FDA may be called upon to consider the patient's physician as the sponsor for a study involving the patient. If the sponsor of the already ongoing study is not willing to make the product available, it is impossible for the single patient study to proceed even though the Agency has no objections to the treatment. In considering such cases, the Agency is bound by strict rules of confidentiality governing the types of information it can disclose to a physician about the sponsor's product and development data.

We understand that there have been instances where sponsors who did not want to provide access to an experimental product under a single patient IND told the patient or requesting physician that FDA had refused the request, when we had not. We also are aware of situations where patients or physicians have sought access to a particular investigational product without knowing all of the relevant information that needs to be considered in deciding whether use of the product would be appropriate for a particular patient. Our ability to fully disclose such information to the patient, her physician, or, for example, a member of Congress who inquires on her behalf, is dependent

largely on the sponsor's willingness to disclose confidential commercial information.

One may ask why FDA is involved in this process at all. We believe that we play a crucial role and one that provides a unique and vital service to the patient, the physician and the American public. In the typical single patient IND situation, especially those involving emergency IND requests, the patient's physician may have only very limited information about the investigational therapy being requested. The Agency's primary role in deciding whether to allow a single patient IND to proceed is to determine whether use of the therapy in the particular patient involved would be reasonable. In making that determination the Agency considers a variety of factors, including: the patient's diagnosis; the evidence of potential benefit and toxicity from clinical situations; the availability of therapies that are likely to be curative or highly beneficial; the sufficiency of information on dosage and toxicities; and whether the patient is being provided timely, complete and useful information as part of the informed consent process. We are mindful, as well, that the clinical trial process -- which is vital to understanding the clinical utility of a product, and which is therefore vital to all patients with the disease -- not be impacted negatively by the availability of the product outside the clinical trials.

Although, for the most part, the Agency does not keep records of denials of single patient or emergency IND requests received orally, an informal survey of the drug and biologic divisions suggests that such denials are rare. In the case of an emergency, it is common for FDA to give a physician permission over the telephone to begin treatment and to allow the paperwork to be completed later.

D. THE OFFICE OF SPECIAL HEALTH ISSUES

Given the frustrations that patients and their families experience in being one step removed from what may be life or death decisions involving the availability of potentially helpful therapies, the Agency created the Office of Special Health Issues (OSHI). The center piece of the activity in OSHI is the patient with a life threatening disease, most often cancer and AIDS. Most callers want information about treatments currently being researched. Although we are constrained by statutory and regulatory requirements from disclosing proprietary information about products under development, we are able to talk with patients about any treatment that appears in public access data bases, such as the National Cancer Institute's PDQ data base which contains more than 1500 cancer clinical trials.

Our goals in serving patients with life threatening diseases and their family members are straightforward:

1) Promptness (returning patients' and family members' calls within 24 hours);

2) Accessibility (listening to the caller's concerns and giving him or her as much time as he or she needs);

3) Education (about the drug approval process and his or her options);

4) Assistance (providing additional information to the patient or family member that may be helpful, e.g. other sources of information).

The nature of the calls vary greatly. Sometimes they are simple calls in search of information on clinical trials. Often, the calls are more complex, such as distraught patients or family members seeking access to a drug which has not been approved.

These calls, by their nature, are very difficult ones. OSHI has a trained empathetic staff dedicated to providing as much assistance as possible to patients and family members undergoing extremely difficult times. It is our responsibility to remain rational and reasonable and most of all compassionate. The staff explains the steps to follow in requesting access to unapproved products. Patients and family members are encouraged to call back as often as needed to get their questions answered or express their point of view. OSHI receives approximately 1000 calls from patients and family members annually requesting access to unapproved products.

OSHI also works within the Agency to assist with patient and consumer requests to become more involved with the drug approval process. There is a web page which is updated regularly with information on AIDS and cancer issues. Specifically, there is information on patients and clinical trials, product approvals, meetings, and other articles of interest to this constituency. This web page receives approximately 27,000 hits per month.

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Sometimes, there are persons who refuse to participate in the statutory scheme. This puts patients at risk of using unproven products and also denies to all patients the knowledge of therapies that actually may work. Our challenge today is to find ways to speed remedies to patients, without sacrificing the protections established in the law. Collectively, we need to address how to promote research on possibly effective remedies where market incentives may not work.

We have faced, and met, many challenges in keeping pace with unprecedented medical and scientific breakthroughs and the evolving and increasing expectations regarding access to medical products and meaningful health information. An individual with a life-threatening and chronic illness for which there is no adequate remedy has a compelling case. As

compelling as an individual case is, however, the cost of providing individual access cannot be to sacrifice the system that ultimately establishes whether therapies are safe and effective. It is essential to preserve the system of controlled clinical trials that provides the information necessary to make the final determination on the safety and effectiveness of unapproved products. The two concepts, the protection of public health and compassion and respect for individuals, can, and must, coexist.

II. CURRENT ACTIVITIES REGARDING "ALTERNATIVE" AND "COMPLEMENTARY" PRODUCTS

FDA has undertaken a number of initiatives to address some of the new and varied challenges posed by alternative and complementary products. I would like to share some examples with you today.

A. FDA COLLABORATION WITH THE NIH OFFICE OF ALTERNATIVE MEDICINE

Since establishment of the Office of Alternative Medicine (OAM) at the National Institutes of Health (NIH) in 1992, FDA has worked closely with this new office. In addition to collaborating with OAM in the organization of a series of conferences, FDA also has provided assistance to OAM and to

others interested in examining alternative or complementary products. FDA has been involved in clarifying existing regulations and policies, and in the design and conduct of research studies.

FDA and OAM have held ongoing meetings to discuss issues of mutual interest. At these meetings, Government and non-Government participants discussed current policies and cost implications of reimbursement for alternative medicine and medical management. The discussions touched upon how one can make the determination that a particular modality is safe and effective. There also has been consistent representation of FDA at the meetings of OAM's advisory panel since 1992, and at the meetings of the Alternative Medicine Program Advisory Council.

B. BOTANICALS

There is increasing public interest in botanicals. Botanicals include herbal products made from leaves, as well as products made from roots, stems, seeds, pollen or any other part of a plant. Many of these products are marketed legally as dietary supplements. Botanical products used as "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals" would be considered "drugs," under the FDC Act.

NIH has filed several INDs for botanical products being studied under NIH grants, as indicated above. The announcement of the filing of these IND's raised the public's awareness of the issues involved in the medicinal use of unpurified forms of botanicals.

Botanical products pose some issues that are unique to this class of product, including the problem of lot-to-lot consistency. These unpurified products, which may be either from a single plant source or from a combination of different plant substances, often are thought to work through mechanisms or "active principles" which are either unknown or undefined. For these reasons, the exact chemical nature of these products may not be known, as it is with small molecular weight drugs. In addition, issues of strength, potency, shelf-life, dosing and toxicity monitoring need to be addressed.

Currently, FDA is developing a guidance document on botanicals used as "drugs." This document will address certain types of information to meet statutory requirements for an IND for a botanical. On another track, the Agency is considering requests to accept foreign marketing data for products that might be best suited for sale as over-the-counter products. This mechanism could allow the American public much quicker access to many types of products, including botanicals, currently marketed abroad.

Many workshops have been held over the past several years to examine the use of botanicals for treatment of health conditions. For example, FDA and NIH collaborated on a conference held in late 1994. This conference, the *Symposium on Botanicals: A Role in U.S. Health Care?*, attended by more than 450 participants, brought together representatives of United States and foreign herbal, food, and pharmaceutical industries, their trade organizations, researchers and practitioners of herbal medicine, academia, and regulatory and other Government agencies.

The conference identified and addressed issues concerning the use and development of botanical products in the United States. Participants discussed such questions as: 1) What are botanicals and how are they currently used? 2) How could we know that botanicals work? 3) How can we know that these products are safe? 4) How can we ensure that botanical preparations will be of good quality? 5) How do regulations affect the marketplace and impact the cost of health care? Reports of this conference have been published. There was consensus regarding the need for improved quality control, including proper plant classification and nomenclature, and control of growth, harvest conditions, and other parameters important for lot-to-lot product consistency. If a product varies greatly, as can occur with botanicals, it is critical to obtain lot-to-lot product consistency. Without this, it is

difficult to determine if the product is causing the change in a patient's condition, or the change is related to some other factor. The conference concluded that safety of these products is difficult to evaluate with certainty in the absence of quality control standards for the product and effective monitoring for adverse effects associated with product use.

C. ACUPUNCTURE

In 1994, FDA and NIH identified the need to examine the regulatory status of acupuncture needles. Acupuncture needles were still considered investigational in the United States and, as a result, had to be labeled as investigational and could not be advertised or promoted. On March 29, 1996, after reviewing the data on acupuncture needles, the Agency reclassified the needle from a Class III medical device (a category in which clinical studies are required to establish safety and effectiveness) to a Class II medical device (a less restrictive category for which regulatory controls, in this case, focused on matters such as sterility and needle breakage). This change effectively removed the needle from the "investigational" category, established some minimum standards for manufacturing and labeling and confirmed their safety.

III. PROTECTING THE PUBLIC HEALTH: FDA'S CONCERNS ABOUT H.R. 746

Our primary concern with "The Access to Medical Treatment Act" (AMTA), H.R. 746, is that it would weaken the protections of the FDC Act. Specifically, it would limit FDA's ability to help assure reasonable safety, effectiveness, informed consent, and scientific data collection. In assessing the impact H.R. 746 would have on the Agency and, more importantly, on the consumer, we must begin with an understanding that the consumer protection afforded by the FDC Act is grounded in the ability of the Agency to make science-based health and safety decisions about the medical products offered in the United States. In turn, these science-based health and safety decisions are a cornerstone of the informed consent process on which patients rely in deciding what types of medical treatment to pursue. We know from experience what happens to consumers left to fend for themselves in a health marketplace.

FDA's original law, the Pure Food and Drug Act of 1906, was passed by Congress as a result of unhygienic conditions in Chicago's meat-packing plants. The law, however, did little to control the use of dangerous and fraudulent drugs and devices. It took a catastrophic incident to propel further action. In 1937, more than 90 people in 15 States, almost all of them children, died as a result of taking a liquid dosage form of

the drug sulfanilamide. This new liquid formulation, Elixir Sulfanilamide, contained diethylene glycol (used commonly as antifreeze) and was marketed without benefit of any toxicity testing. At the time, the law did not require safety studies on new drugs. The Elixir of Sulfanilamide scandal followed closely on the heels of another tragedy. In the 1930's, another drug, dinitrophenol, widely used for weight reduction, resulted in deaths, as well as hundreds of cases of blindness, agranulocytosis (a potentially fatal blood disorder), and other serious adverse reactions.

These incidents hastened the enactment of the FDC Act in 1938, which considerably expanded consumer protection by requiring safety testing of new drugs prior to approval for marketing. In short, in 1938, Congress told companies that they had to test their drugs for safety and submit an application to FDA before a drug could be legally marketed. Under this law, FDA had the necessary authority to keep products such as thalidomide off the market for use during pregnancy to reduce nausea (which caused phocomelia, a severe limb deformity in exposed fetuses). Consequently, the American public was spared enormous suffering. Of note, thalidomide is now under investigation, under multiple INDs, for a variety of other indications for populations that may benefit. The authority to regulate biologics and the responsibility for protecting the public against communicable diseases are contained in the

Public Health Service (PHS) Act. The regulation of biological products was administered by NIH until 1972 when the regulation of biologics was transferred to FDA.

In 1962, Congress set in place the second cornerstone for our public health and consumer protection efforts. Congress stated that before a company could legally market its drug to patients, the company had to test the drug and show that it was both safe *and effective*. Effectiveness had to be shown through adequate and well-controlled trials, including clinical trials, which represented the scientific standard for evidence in 1962, and still does today. In 1976 and 1990, Congress again amended the law to establish a regulatory scheme designed to help ensure that medical devices also would be safe and effective. Also, a major amendment to the PHS Act, the National Childhood Vaccine Injury Act of 1986, extended FDA's authority by authorizing FDA to recall biologics.

Finally, as recently as November of last year, Congress again amended the FDC Act and related statutes through enactment of the "Food and Drug Administration Modernization Act of 1997." This legislation was the culmination of over 2 years of hearings, oversight and other legislative activity assessing the Agency's performance and reviewing its statutory mandate. Congress specifically rejected the arguments of those who urged that the fundamental requirements of the statute -- that drugs

and devices be found to be safe and effective before they can be marketed -- be lowered or eliminated in order to open the marketplace. Moreover, as noted above, the expanded access and expedited approval processes already being used by the Agency were codified.

These laws were designed to protect the public health, and they have done a good job. At the same time, the laws are flexible and allow desperately ill patients access to unproven treatments and drugs. While FDA shares with the sponsors of H.R. 746 interest in expanding the options for medical treatment for the American public, we must take care to do so in a way that does not lower existing public health protections.

Patients want to make informed choices about medical treatments, whether conventional or alternative and complementary. While H.R. 746 addresses access to unproven products, the bill, as written, does not adequately address the need for accurate information on the safety and effectiveness of such unproven products.

A. PROTECTING THE PUBLIC FROM UNSAFE PRODUCTS

Unlike current law, H.R. 746 does not require a company to test a drug or device before selling it to humans. There will be no

teratogenicity tests, which give information about the potential toxicity of drug products, like that of thalidomide, so that teratogenic drugs will not be given to pregnant women; there will be no tests to determine whether the drug causes cancer in animals; there will be no acute toxicity tests, of the kind that keep many drugs out of human studies altogether; there will be no tests to determine whether the drug causes acute damage to the liver or kidneys; and there will be no assessment of chronic animal toxicity prior to chronic exposure of humans.

There is also no requirement to study drugs carefully in humans prior to widespread use in treatment. A very significant percentage of all drugs tested in humans are dropped from further development because of unacceptable toxicity. This toxicity is not apparent initially, but often is discovered during early clinical testing.

Medical history is replete with examples of useless and sometimes even dangerous products and procedures that were used based on anecdotal information, not evidence, and were thought for years by many clinicians to be effective. For example, in the 1940's and 1950's, it was common clinical practice to administer pure oxygen to premature infants. It took over a decade to discover that the treatment was causing blindness. By that time, approximately 10,000 babies had been made blind.

If clinical trials and systematic data collection and analysis had occurred early in the use of this oxygen treatment, these babies may have been spared their eyesight. After the effectiveness standard was established in 1962, FDA worked with the National Academy of Sciences National Research Council to review the effectiveness of drugs marketed for various claims in the United States before that effectiveness standard was established. Of the 3,443 drugs on the market, 1,124 were pulled from the market because they were not effective for their intended use.

Under current law, the burden is on the sponsor of a product to prove that the product is safe and effective. In essence, this legislation would shift that burden to the Government. Under this bill, a product would be assumed safe unless the Government could show that it "poses an unreasonable and significant risk of danger." In addition, it appears that such a showing would need to be made on a product-by-product basis. This would make it enormously difficult and resource intensive, and in many cases might require laboratory and research capabilities that do not exist, to regulate the marketplace effectively.

In addition, we are concerned about products that are labeled "natural" or from an herbal source that may be assumed to be safe under H.R. 746, but could pose serious risks. For

example, FDA published a proposed rule last year to reduce the risks with dietary supplement products containing ephedrine alkaloids by, among other things, limiting the amount of ephedrine alkaloids in such products and requiring labeling to give adequate warning and information to consumers. (62 Federal Register 30678) The proposal also articulates FDA's policy that products marketed as alternatives to illicit street drugs are drugs, not dietary supplements.

The ephedrine alkaloids in dietary supplements usually are derived from one of several species of herbs of the genus Ephedra, sometimes called Ma huang or Chinese Ephedra. Ephedrine alkaloids are amphetamine-like compounds with potentially powerful stimulant effects on the nervous system and heart. Since 1994, the Agency has received and investigated more than 800 reports of adverse events associated with the use of dietary supplement products which contained, or were suspected of containing, ephedrine alkaloids. Reported adverse events range from episodes of high blood pressure, irregularities in heart rate, insomnia, nervousness, tremors and headaches, to seizures, heart attacks, strokes, and death. Most events occurred in young to middle aged, otherwise healthy adults, using the products for weight control and increased energy.

The proposed rule was developed based on FDA's review of its adverse event reports, the scientific literature, and public comments reviewed by the Agency, including comments generated by an October 1995 advisory working group public meeting and an August 1996 public meeting of FDA's Food Advisory Committee. These experts suggested a number of steps the Agency might take to reduce injuries associated with use of dietary supplements containing ephedrine alkaloids. If implemented, the proposed rule will reduce the risk of adverse events for consumers who use these products.

H.R. 746 attempts to address some of these concerns by requiring that patients be informed of "any reasonably foreseeable" side effects. The difficulty is that there will be no way to know about potential side effects without systematic testing, data collection, and evaluation. In effect, patients will not have the information necessary on which to make informed consent.

Moreover, H.R. 746 effectively removes any requirements for reporting adverse events for treatments or products that are used to treat serious medical conditions. The bill only requires practitioners to report medical treatments that are a "danger" to the patient. The bill's definition of "danger" only includes negative reactions that are "more serious than reactions experienced with routinely used medical treatments

for the same medical condition or conditions." Even well-studied drugs, biologics, and devices that are "routinely used" to treat patients can, in themselves, cause significant adverse effects in some patients. For example, many conventional drugs "routinely used" to treat cancer patients can have serious or life-threatening effects. Without the comprehensive collection of data on adverse events, there will be no way of knowing whether a product is safe, or for that matter, dangerous.

B. KNOWING WHETHER PRODUCTS WORK AS INTENDED

We are concerned that H.R. 746 would significantly diminish incentives for practitioners and manufacturers to gather data on whether products are effective for their intended use. Based on substantial scientific experience, it is critical to obtain data on specific uses of products and to analyze those data so that we can know if a product will work as intended. Encainide and flecainide are two drugs that unfortunately illustrate this point quite dramatically. These drugs were approved by FDA only for the treatment of serious, potentially fatal, abnormal heart rhythms or rhythms that were severely symptomatic. The labeling for the drugs specifically warned that effectiveness and safety were not established for people with recent heart attacks. These drugs appeared to be safe and effective anti-arrhythmia drugs, and therefore, many physicians prescribed them for recovering heart attack victims with mild,

non-symptomatic rhythm abnormalities, hoping to lower their risk of sudden death (which is increased in people with mild heart rhythm abnormalities). This practice came to an abrupt halt when a large clinical trial sponsored by the NIH found that these drugs, while effectively suppressing the abnormal rhythm, were actually killing heart attack victims, not helping them. Encainide and flecainide increased the sudden death rate in recovering heart attack patients by two and one-half fold.

We are concerned that under this bill limited data would be collected on the effectiveness of any treatment and ineffective, or even unsafe, treatments could become widely used. While the bill requires that OAM be informed of beneficial medical treatments and the Secretary of Health and Human Services be informed of dangerous medical treatments, there is no requirement for systematic data gathering or testing. The bill is silent on the extent of data gathering and analysis a practitioner must perform in order to inform OAM. Systematic data collection must be conducted in order to obtain a clear understanding of the range of benefits a patient may gain from a treatment or combination of treatments.

We do not believe that the bill's labeling and advertising restrictions are adequate to assure patients will not be misled into accepting unsafe and/or ineffective treatments. From FDA's experience, advertising, as discussed in H.R. 746, is not

necessary to achieve wide use of a medical treatment. We know that widespread use of medical products or treatments by health care practitioners is not dependent on "advertising" claims, but can occur simply through professional meetings, seminars, conventions, articles, and word-of-mouth communications. Information technology, such as the Internet, have increased the speed and volume of such informal communication many fold. Moreover, FDA has found that often seemingly independent seminars, conventions, and press conferences have, in fact, been sponsored by the companies whose medical products were discussed at the meetings.

Further, by allowing for the informal marketing of treatments without any evaluation, this bill actually creates a disincentive to testing. In fact, under the definition of "seller," H.R. 746 specifically excludes the health care practitioner who receives payment for a treatment. Allowing wide dissemination of a treatment and subsequent widespread use combined with little accountability or liability, significantly reduces the incentive for manufacturers and health care practitioners to conduct studies of safety and effectiveness.

C. INFORMED CONSENT

Let us now turn to the informed consent provisions in the bill. It is well accepted that informed consent exists only if the

patient is given information about the risks and benefits of a treatment before making a decision. Under current law, a patient is not considered to have given informed consent unless the patient has been advised, in writing, among other things, of the reasonably foreseeable risks or discomforts to the patient; a description of the potential benefits that might be expected, either to the patient or to others; a disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the patient; and an explanation of who will pay for the patient's care if the patient is harmed by the experimental treatment. Furthermore, FDA's informed consent regulations are intended to work in concert with Institutional Review Board oversight.

While H.R. 746 attempts to include these provisions, one must question whether informed consent can truly be achieved without consistent collection and analysis of data. Under H.R. 746, a patient will have little or no information upon which to base a decision, because no preliminary work on possible risks and benefits will have been required.

Informed consent is a particularly important matter for the acutely ill as well as for those suffering from a chronic illness. H.R. 746 does not preclude practitioners from either unknowingly or intentionally misleading patients with little or inadequate information. This increases the chance that

patients will be subjected to unorthodox testing of new medical treatments without adequate protections or information.

D. REMOVAL OF DANGEROUS PRODUCTS

We also are concerned that under this bill the only authority the Secretary has when she does learn of a dangerous therapy is to publicize the fact. Now, when a product is determined to be unreasonably dangerous, we can remove the product from the market. This legislation raises serious questions about FDA's authority to remove dangerous and/or fraudulent products from the market. Rather, the Federal Government would have to expend significant resources to engage in an ongoing educational campaign about the dangers of the treatment so that health care practitioners and their patients will not make the same harmful mistake over and over again. This brings us back full circle to the years before the 1938 FDC Act, when FDA could do little to protect the public from dangerous and/or fraudulent drugs and had no authority to require the submission of reliable information before a drug could be legally marketed.

IV. CONCLUSION

We have learned a lot about expanded access and expedited product approval from the various programs we have implemented

to provide access to unapproved products. We have learned that uncontrolled expanded access cannot co-exist with the need to pursue controlled clinical trials, which provide the information necessary to serve the interests of everyone. The best interest of the patient, of all patients, is not only to provide access, but also to complement it with the collection of information necessary to lead to a demonstration of safety and effectiveness. We also have learned that it is possible to make promising products available before approval in ways that protect the patients, gather valuable information, and permit the timely completion of the clinical trials. Patients, physicians, sponsors, and FDA all want the same thing -- safe and effective products to treat patients with serious and life-threatening diseases. We believe that the role FDA has played in expanding and expediting access has permitted, and will continue to permit, the most critically ill patients to have access to the most promising products.

There is always more that remains to be done. There may be more FDA could do to make physicians aware that there are mechanisms through which they may be able to treat patients with promising experimental products. FDA also must explore mechanisms to make physicians and patients more aware of potentially beneficial products that are available currently under expanded access. Equally, we must explore mechanisms to communicate to physicians and patients how much accurate

information is known and how much is unknown about a particular experimental drug. There must be processes to evaluate and disseminate data rapidly on new products, both unapproved and approved, in a manner that is credible to patients and useful to physicians.

It seems that there also are questions to be addressed that go beyond the scope of FDA's authority or particular expertise. There are questions about how to create the market incentives that may be necessary if existing, unpatentable products are going to be tested. The Congress looked at that question in addressing the need for private investment in the development of products to treat so-called orphan diseases, those which affect populations that are too small to attract standard commercial investment. There are questions about how to encourage sponsors and manufacturers to be willing more frequently to provide expanded access. There also are questions about how we as a country spend our scarce public health research dollars, and whether more of those dollars should be spent understanding the safety and effectiveness of alternative and complementary treatments. We certainly would be willing to work with the Committee in examining such questions.

Fundamentally, you ask the question where should we, as a matter of public policy, draw the balance between public health

protection and personal autonomy. We think Congress has drawn that balance correctly in the FDC Act.

FDA shares the Committee's concern about making promising new treatments available to the public in a timely manner. To that end, we have tried to be responsive and compassionate to individual patient requests for products for which the necessary studies have not been completed. Our core mission remains to help ensure that there is adequate scientific evidence that new treatments are safe and effective as the public deserves and the law requires.

Thank you for the opportunity to testify.

APPENDIX

I. EXPEDITING DEVELOPMENT, REVIEW AND APPROVAL OF NEW PRODUCTS

FDA has implemented mechanisms designed to increase access to new drugs, biologics, and medical devices by expediting their development, review and approval. FDA has three such programs for human drugs and biologics: expedited review, priority review and accelerated approval. Section 112 of FDAMA amends the FDC Act providing explicit authority for FDA to approve a drug based on surrogate endpoints, i.e., accelerated approval.

A. Expedited Review

FDA assists companies to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses under procedures contained in 21 CFR Part 312, Subpart E. Recognizing that such drugs are often approved with a smaller safety data base than drugs with less significant clinical benefits, FDA is prepared to assist sponsors in designing definitive clinical trials to evaluate safety and effectiveness at the earliest possible stage point in the drug development.

Subpart E emphasizes that while the statutory standards for safety and effectiveness apply to all drugs, the many kinds of drugs and range of uses compel flexibility in applying the standards. In general, patients and physicians are willing to accept increased risks from products that treat life-threatening or severely debilitating diseases. If a beneficial effect is demonstrated, approval may be warranted without the additional data and usage information developed during Phase 3 studies. In these instances, additional data, long-term effects, and differences in response among subsets of the population, may be obtained after approval. In the meantime, patients with life-threatening diseases are afforded direct access to the drug.

Since the effective date of the Subpart E regulations, there have been 43 new drug applications (NDA) approved that had been designated under Subpart E while in the investigational new drug application (IND) stage. Of these NDAs, 27 were for cancer and AIDS, and 16 were for indications other than cancer and AIDS, including several for conditions that occur in patients with cancer or AIDS. It should be noted that almost all cancer and AIDS therapies are handled under expedited review in accordance with the Subpart E procedures, even if the sponsor has not requested the designation.

B. Priority Review

To further assist in speeding the review of NDAs, BLAs and effectiveness supplements, FDA has implemented a review priority classification. Upon initial receipt, applications are classified as either priority or standard based on the estimate of therapeutic preventive or diagnostic value. A priority designation is intended to direct overall attention and resources to the evaluation of applications for such products that have the potential for providing significant preventive, diagnostic, or therapeutic advances, particularly for patients with serious or life-threatening illnesses. Such a classification will determine an overall approach to setting review priorities.

C. Accelerated Approval

In December 1992, FDA published final regulations outlining a new procedure for accelerated approval of certain new drugs or biological products based on the product's effect on an objective surrogate endpoint that is reasonably likely to predict effectiveness of the product. (21 CFR Part 314, Subpart H and 21 CFR part 601, Subpart E). In addition, FDAMA provides explicit authority for FDA to approve a drug based on surrogate endpoints. A surrogate endpoint is a laboratory effect or other clinical measurement that does not itself directly measure clinical benefit but is thought to correspond to clinical outcome. Approval can be based on such an endpoint if it is scientifically reasonable to believe that an effect on the surrogate will correlate to a clinical benefit. For example, lowering blood pressure or cholesterol in patients with cardiovascular disease is desirable only if lower blood pressure and/or lower cholesterol are correlated with decreased rates of stroke, heart attack, or other clinical events, not because a low blood pressure reading or lower cholesterol is good in and of itself. Well-established surrogate endpoints have been the basis of approval of many drugs in the past. Under accelerated approval, less well established surrogates also can be the basis of approval if they are reasonably likely to predict benefit.

The accelerated approval regulations apply to products used in the treatment of serious or life-threatening illnesses that appear to provide meaningful therapeutic benefits over existing treatments. When approval is based on substantial evidence of an effect on a surrogate endpoint, the sponsor may be required to conduct additional adequate and well-controlled studies that are necessary to verify that the effect on the surrogate marker represents improved clinical outcome. Often, the postmarketing studies will be underway at the time of approval. The procedures also allow for a streamlined withdrawal process if, for example, the postmarketing studies do not verify the drug's anticipated clinical benefit, or if there is other evidence that the drug product is not shown to be safe and effective.

Because effects on surrogate markers usually can be demonstrated with studies that are much smaller and much shorter than studies using endpoints like survival, these efforts have allowed drugs for serious and life-threatening diseases to be marketed much sooner than normally would be the case. There is always the risk that the effect on the surrogate, despite its reasonableness, will not reflect an ultimate clinical benefit, but in these urgent cases, that risk appears acceptable. Since its inception, there have been 17 drugs and biologic products that have received accelerated approval under this procedure.

Importantly, FDA regulations also emphasize several safeguards for the protection of human subjects, including the requirement for informed consent, Institutional Review Board (IRB) review, conduct and review of animal studies prior to human testing, IND safety reports and updates, and adverse drug reaction reports.

II. EXPANDED ACCESS TO, AND ACCELERATED APPROVAL OF, CANCER THERAPIES

In March 1996, building on FDA's accelerated approval program, President Clinton and Vice-President Gore announced a new FDA initiative to improve patient access to promising new cancer therapies. Under this initiative FDA is taking four steps to speed the approval of promising therapies for treating cancer. These include:

- Shortening approval times for cancer treatments by recognizing that tumor shrinkage is often a reasonable surrogate endpoint of a treatment's effectiveness in patients with otherwise untreatable cancer. Basing approval on evidence of tumor shrinkage--which can be more easily and quickly demonstrated--can speed up access to promising new therapies (compared with waiting for evidence of improvement in survival time);

- Encouraging pharmaceutical companies to submit expanded access protocols in the United States for cancer therapies that have been approved by recognized foreign regulatory authorities, thus helping to make promising cancer therapies approved by foreign countries available to cancer patients before the products are approved in the United States;

- Improving the product review process by ensuring that all FDA cancer therapy advisory committee meetings include an ad hoc member who has personal experience with the illness for which a new product is being considered; and,

- Making it easier for investigators to test new uses for cancer therapies already on the market by reducing the number of IND applications filed for additional studies of already approved therapies.

FDA undertook these initiatives after careful consideration of suggestions and advice offered by cancer patients and their advocates, pharmaceutical industry representatives, and physicians and researchers about how to speed access to cancer therapies. FDA's goal is to improve significantly patient access to promising cancer treatments without compromising patient safety or the requirement that marketed drugs be proven safe and effective before they are sold.

III. EXPANDING ACCESS TO INVESTIGATIONAL PRODUCTS

The ideal mechanism for a patient to receive a promising but unproven drug is as a participant in a controlled clinical trial. Such trials provide a range of patient protections and benefits (for example, IB. review, informed consent, free product or treatment, and FDA review of pre-clinical data) and maximize the gathering of useful information about the product thereby benefitting the entire patient population. It is not always possible, however, for all such patients to enroll in controlled clinical trials. In this situation, FDA believes that it is possible, and appropriate, to help make certain promising, but unproven, products available to patients with serious and life-threatening illnesses. This should be done in a way that poses neither an unreasonable risk to the patient nor an unreasonable risk of losing valuable information about the effect of the drug.

While the phrase "compassionate use" is commonly used to describe some of the ways of making unapproved products available, there is no FDA regulation or policy defining a "compassionate use." Compassion, however, should be, and is, an element of all our activities. FDAMA has codified certain FDA regulations and practices regarding expanded patient access to experimental drugs and devices. The new legislation addresses three expanded access procedures with respect to: 1) emergency situations; 2) individual patient access to investigational products intended for serious diseases; and 3) treatment investigational new drug applications and treatment investigational device exemptions. The Agency is in the process of reviewing current regulations and practices to assure coordination with FDAMA. There are a number of mechanisms FDA has used to provide access to promising investigational therapies. These mechanisms fall under a variety of terms, including: treatment INDs; treatment protocols; single patient INDs; emergency INDs; open label protocols; protocol exemptions; continued availability of investigational devices; special exceptions; open label extensions; parallel track; emergency use of unapproved medical devices; and treatment Investigational Device Exemptions (IDE).

A. Treatment INDs or Treatment Protocols

As noted, the most useful mechanism for access to unapproved drug or biologics therapies is for patients to be enrolled in a

controlled clinical trial under an IND which may benefit patients' health as well as contribute to the data necessary to determine whether the drug or biologic is sufficiently safe and effective to merit final marketing approval. Some patients who might benefit from access to an investigational new drug, however, might not be enrolled in a controlled clinical trial. If there is sufficient evidence available to provide a reasonable basis for concluding that the drug or biologic may be safe and effective for patients with a serious or immediately life-threatening disease, one mechanism through which patients can have access to the drug or biologic prior to approval is a treatment protocol or treatment IND.

The most explicit expanded access mechanism in the regulations is the treatment IND or treatment protocol. The final rule on treatment protocols or treatment INDs was issued in 1987 and is found at 21 CFR Section 312.34. These regulations were codified in FDAMA. This mechanism is intended explicitly to facilitate the availability of promising new drugs and biologics to desperately ill patients as early as possible in the development process before general marketing begins.

Although a primary purpose of a treatment IND is to allow treatment, this mechanism also is intended to obtain additional data on the drug's safety and effectiveness under certain criteria: the drug must be for a serious or immediately life-threatening disease; the available data must provide a reasonable basis for concluding that the drug or biologic may be effective for its intended use; there must be no comparable treatment alternative; the controlled clinical trials of the drug or biologic must be completed or underway; and the sponsor must actively be pursuing marketing approval.

Since the treatment IND procedures were developed, FDA has designated 40 drug or biologic investigational products for such early availability, and 36 of the products have proceeded to marketing approval or licensure under NDAs or product license applications (PLAs). Of the products approved, 11 have been for cancer, 11 for AIDS or AIDS-related conditions, and the remainder for a wide variety of other severely debilitating and life-threatening diseases, including obsessive compulsive disorder, severe Parkinson's Disease, multiple sclerosis, respiratory distress syndrome in infants, Gaucher's disease, diabetes, amyotrophic lateral sclerosis or ALS (Lou Gehrig's disease), and others.

B. Single Patient/Compassionate INDs

As early as 1968, an FDA mechanism, informally known as a "compassionate use" study, provided patients who were not participating in the controlled clinical trials access to investigational drugs. The "compassionate use" study could be

conducted either under a separate or existing IND. Such studies were not formal controlled trials, but they permitted use of an investigational drug under a protocol for an individual patient or patients, or for an early exploration of a novel idea. As noted previously, FDAMA addresses expanded access to unapproved therapies in emergency situations and in the case of individual patients who seek access to investigational products intended for serious diseases. An FDA working group is reviewing existing regulations and practice to assure coordination with FDAMA. Currently, the mechanisms used to provide expanded access include: single patient/single use IND, an emergency use IND, an open label protocol, or an open label extension. The term emergency IND refers to single patient uses for which there is not enough time for the treating doctor to file the required IND paperwork before administering the investigational product. In such cases, FDA can authorize the use of the product over the phone.

Under current practice, single patient/single use (non-emergency) and emergency INDs often are allowed to proceed when a physician determines that a particular unapproved therapy might be of benefit to a particular patient under his or her care for whom other options do not exist. For a treating physician to administer an unapproved product to a patient, the following conditions are necessary: a) the patient must be informed about the relevant circumstances about the drug and consent to take the product; b) the physician must be properly licensed and she/he must agree to administer the product and be responsible for monitoring and reporting data on the patient's use of the product to the sponsor; c) the IB. must approve the proposed single investigation (note that in emergency situations, the physician may notify the IB. promptly but after treating the patient); and d) the manufacturer/sponsor must be willing to provide the product without charge (unless the sponsor has applied for and FDA has allowed charges for cost recovery). Each of these conditions is critical to maintaining the dual goals of providing the patient with a promising product, and protecting the patient from potentially unsafe or ineffective products. There is a minimal amount of paperwork required to process a request for a single patient or emergency use IND.

Emergency INDs are treated as matters of medical urgency and are intended to be handled expeditiously by FDA. In the vast majority of emergency INDs, FDA renders a decision on such requests within a few hours. There are some rare exceptions when the particular therapy is completely unknown and may require additional information. These usually are approved within 48 hours.

For certain unapproved products, FDA has set up internal procedures to facilitate single patient IND requests. One example of this is the process for single patient IND requests

for thalidomide. Physicians are put in touch with a consumer safety officer within the relevant reviewing division; the consumer safety officer helps the physician understand the IND process to facilitate completion of the IND application. Some of the information required includes the name of the drug supplier, the patient's disease history and prior therapies, a detailed protocol of treatment, the patient's informed consent, and the investigator's qualifications.

C. Open Label Protocol

Patients may be able to gain access to an unapproved product through what is termed an open label protocol. An open label protocol allows patients to receive the drug while some safety information is collected, but these patients have no control group. In effect, these are similar to single patient INDs, but multiple individuals can be processed through one general request by the drug sponsor. When many patients are in need of an unapproved therapy and the above-mentioned conditions pertain [e.g., a physician judges that a particular unapproved therapy might be of benefit to a particular patient for whom other options do not exist; there is sufficient evidence of safety and effectiveness to support the use of the investigational product; and the sponsor of the unapproved new drug or biologic has agreed to provide the drug free of charge (unless the sponsor has applied for, and FDA has allowed charges for cost recovery)] the drug or biologic may be available through the open label protocol.

Many thousands of patients have received unapproved therapies by this means. For example, there have been several large open label protocols for anti-retroviral drugs (e.g., anti-HIV drugs) which have involved tens of thousands of patients.

Open label extensions provided another mechanism for gaining access to unapproved products. These extensions enable those patients who received a therapeutic response during a controlled clinical trial under an IND that has ended to continue the investigational drug treatment.

There are a number of situations in which a patient who wants access to an unapproved drug is unable to receive the drug. In many cases a sponsor is unwilling to provide the product. Patients sometimes are confused by this situation and misinterpret a company's unwillingness to provide the product as an FDA action. Much less frequently, the cause may be FDA's concern about the risk to patients because of the nature of the product. Generally, if a physician makes the request and a sponsor agrees to provide the product, FDA does not object to the study proceeding.

At times, there may be relatively little evidence supporting the usefulness of the drug for the particular indication, but its use may be considered appropriate because there is no alternative for the particular condition. Physicians may always contact FDA to propose such a use for a specific patient when they believe circumstances warrant. Of course, the company still has to make the product available before a patient can gain access.

D. Protocol Exception/Exemptions

In cases where a patient cannot be enrolled in a protocol because of some factor that makes the patient ineligible to participate in the study, research sponsors or investigators often can make a protocol exception to enroll a patient without including the data on that patient in the report of the results from the controlled study participants. This mechanism is sometimes referred to as a special exception.

E. Parallel Track

Another mechanism, parallel track, is an FDA policy that was formally announced in the Federal Register in 1992 (53 Federal Register 13250, April 15, 1992). This policy allows promising investigational drugs for AIDS and other HIV-related diseases to be made more widely available under "parallel track" protocols while the controlled clinical trials are carried out. The purpose of the parallel track mechanism is to permit access to unapproved drugs for people with AIDS and HIV who are not able to take standard therapy, or for whom standard therapy is no longer effective, and who are not able to participate in an ongoing controlled clinical trials. Included in this mechanism is the possibility of having a National Institutional Review Board to review the ethical access to these products.

There has been one large parallel track program since the policy was implemented that included 12,000 patients. Other anti-HIV drugs have been made available by the open protocol mechanism, as noted above. Given the accelerated rate of approval for many drugs for people with AIDS and HIV and the availability of open label studies, it has not been necessary to use this process in recent years.

IV. ACCESS TO MEDICAL DEVICES

Although the Committee has asked that we concentrate on access to drugs and biologics, we feel that a complete picture requires an overview of other FDA mechanisms to permit access to promising investigational products. Similar procedures for access exist in the Center for Devices and Radiological Health (CDRH) which allow access to investigational devices. Under the CDRH "Continued Availability of Investigational Devices" policy, FDA has worked with sponsors and investigators to facilitate treatment use of

promising or important investigational devices once the core clinical investigation of new devices has been completed. The policy allows additional subjects to be enrolled in the IDE protocol while the marketing application is being prepared by the sponsors and reviewed by FDA. This policy has allowed the collection of additional safety and effectiveness information while providing continued access to promising new devices. FDAMA has codified FDA's practice with respect to expanded access to investigational devices.

A. Treatment Investigational Device Exemption

To formalize an access process for important medical devices and to more clearly define procedures and criteria for treatment use, FDA published a final rule on September 18, 1997, effective January 16, 1998, to allow for treatment use of investigational devices. The regulation is patterned after the drug treatment IND regulations with modifications to account for the differences in the IDE process. FDA anticipates that this regulation will facilitate the availability of promising new devices to patients as early in the device development process as practicable while safeguarding against the proliferation of fraudulent products. This regulation also will ensure the integrity and validity of controlled clinical trials.

B. Emergency Use of Unapproved Medical Devices

In 1985, FDA published a guidance document to address those cases in which an emergency need for an unapproved device had been identified, but the device was to be used in a manner not approved under the IDE; the physician or institution was not approved under the IDE; or no IDE existed. The guidance provides criteria to establish whether an emergency exists. These include instances when: 1) the patient is in a life-threatening condition that needs immediate treatment; 2) no generally acceptable alternative for treating the patient is available; and 3) the need to use the device is immediate because there is no time to use existing procedures to get FDA approval for the use. The physician is expected to determine whether the criteria have been met. The guidance also describes patient protections in these circumstances including informed consent; institutional clearance; the IB. chairperson's concurrence; an independent assessment from another physician; and, authorization from the sponsor if an IDE exists.

C. IDE Protocol Deviations

In addition to the above mechanisms, for diagnostic and therapeutic devices for which there is no satisfactory commercially available alternative and the patient does not meet the clinical protocol requirements, FDA has approved requests to modify the existing protocol to treat single patients who do not

meet the initial protocol requirements. In these cases FDA required the requester to submit a justification for such use and to follow certain patient protection measures.

Dr. FRIEDMAN. In this regard, sir, I would be happy if you would like to submit for the record testimony provided at the hearing that Mr. Waxman mentioned by Deputy Commissioner Pendergast concerning IRB human protection issues if that would be of interest to you as well, sir.

Mr. BURTON. We would love to have that submitted for the record and, without objection, I'll put it in the record.

[The information referred to follows:]

I. INTRODUCTION

Mr. Chairman and Members of the Subcommittee, good morning. I am Mary K. Pendergast, Deputy Commissioner and Senior Advisor to the Commissioner of Food and Drugs, U.S. Food and Drug Administration (FDA). I am pleased to be here today to discuss the Agency's policies with respect to the protection of human subjects in biomedical research. I will discuss the basic structure for human subject protection in the United States, the interconnection between FDA and Department of Health and Human Services (DHHS) regulations, and emerging issues in informed consent, including our exception to the informed consent requirements for those patient populations who are in need of immediate medical intervention but who are unable to give consent because of their medical condition. But first I will set out the protections the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the FDA's regulations afforded to research subjects, and the Agency's mechanisms to monitor and enforce those protections through Institutional Review Boards (IRBs), our Bioresearch Monitoring program, and educational efforts.

II. FDA'S STATUTORY AND REGULATORY BASIS FOR INFORMED CONSENT

The FD&C Act and its implementing regulations are one part of a complex system of safeguards that has been designed to promote the highest ethical principles described in the post-World War II Nuremberg Code, the World Medical Association's

Declaration of Helsinki, professional codes of ethics, and the reports and recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

In the system of safeguards that has evolved over the years, there are multiple levels of protection provided to research subjects. Each participant in a research effort -- the company that sponsors the research, the physician who conducts the research, and the IRB -- is obliged to protect the interests of the people who are taking part in the experiments. The FDA's responsibility is to see that the safeguards are met.

A. Responsibilities of the Research Sponsor

The sponsors of research -- usually, manufacturers or academic bodies, but sometimes individual physicians -- must select well-qualified clinical investigators, design scientifically-sound protocols, make sure that the research is properly conducted, and make certain that the clinical investigators conduct the research in compliance with informed consent and IRB regulations. The sponsor also has the obligation to make certain that any IRB reviewing one of its studies comports with FDA's IRB regulations. Sponsor obligations are set forth in the FDA's regulations that govern the design and conduct of clinical trials, and the requirements for submission of

applications to conduct clinical research (21 CFR Parts 312, 314, 601, 812, 814).

B. Responsibilities of the Researcher

The primary regulatory obligations of the clinical investigator are to: 1) follow the approved protocol or research plan; 2) obtain informed consent and ensure that the study is reviewed and approved by an IRB that is constituted and functioning according to FDA requirements; 3) maintain adequate and accurate records of study observations (including adverse reactions); and, 4) administer test articles only to subjects under the control of the investigator.

The essential core of FDA's informed consent regulations, 21 CFR Part 50, is that the clinical investigator must obtain the informed consent of a human subject or his/her legally authorized representative before any FDA-regulated research can be conducted. The researcher has to make sure that, whenever possible, the study participants fully understand the potential risks and benefits of the experiment before the experiment begins. The information provided must be in a language understandable to the subject, and should not require the subject to waive any legal rights or release those conducting the study from liability for negligence. Specifically, the clinical investigator must give the following information to

research subjects in seeking their informed consent to participate in research:

- A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others which may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records;
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained[1];

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[1]"Minimal risk" in both FDA and HHS regulations means 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

- An explanation of whom to contact for answers to pertinent questions about research and research subject's rights, and whom to contact in the event of a research-related injury to the subject; and,
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (21 CFR 50.25(a))

Depending on the nature of the research, other "additional" elements are required if they are appropriate to the research. These additional elements of informed consent include information about the anticipated circumstances under which the investigator may terminate the subject's participation, any additional costs to the subject that may result from participating in the research, the consequences of a subject's decision to withdraw from the study, a statement that the research may involve risks that are currently unforeseeable, a statement that significant new findings will be provided to the

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routine physical or psychological examinations or tests." (21 CFR 50.3(l), 56.102(i), and 45 CFR 46.102(i)) This definition is a key factor in the HHS regulations in its criteria for when informed consent may be waived. FDA and HHS published a list of categories of research in the 1981 Federal Register that could be reviewed by expedited means when they impart no greater than minimal risk.

subject, and the approximate number of subjects in the study. (21 CFR 50.25(b))

In short, the clinical investigator must tell the human subjects important information about the study and its potential consequences, so that the person can decide whether to be in the experiment. The entire informed consent process involves giving the subject all the information concerning the study that he or she would reasonably want to know; ensuring that the subject has comprehended this information; and finally, obtaining the subject's consent to participate. The process, to be meaningful, should involve an opportunity for both parties, the investigator and the subject, to exchange information and ask questions. It is up to the clinical researcher to make certain that, as best as possible, the person understands the information. To acknowledge that the person has received the information and has consented to the research, FDA also requires the clinical investigator to document in writing that consent was obtained. We recognize that the documentation of informed consent represents only one part of the entire consent process. The consent form itself is an aid to help ensure that a required minimum amount of information is provided to the subject and that the subject consents.

C. Responsibilities of Institutional Review Boards

An IRB is a group formally designated to review, approve the initiation of, and periodically review the progress of, biomedical research involving human subjects. The primary function of IRBs is to protect the rights and welfare of the people who are in clinical trials.

FDA's regulations, 21 CFR Part 56, contain the general standards for the composition, operation, and responsibility of an IRB that reviews clinical investigations submitted to FDA under sections 505(i), 507(d), and 520(g) of the FD&C Act. IRBs must scrutinize and approve each of the more than 3,000 clinical trials that are conducted on FDA-regulated products in this country each year. IRBs must develop and follow procedures for their initial and continuing review of the integrity of each trial. Among other requirements, IRBs must make sure that the risks to subjects are minimized and do not outweigh the anticipated study benefits, that the selection of participants is equitable, that there are adequate plans to monitor data gathered in the trial and provisions to protect the privacy of subjects and the confidentiality of data. The IRB has the authority to approve, modify, or disapprove a clinical trial. If an IRB decides to disapprove a research activity, it must notify, in writing, the investigator of its decision, state its reasons for the decision, and give the researcher an opportunity to respond in person or in writing.

The IRB must approve the informed consent form that will be used. If it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context, the IRB may waive the requirement that informed consent be documented. Where the documentation requirement is waived, however, the IRB may require the investigator to provide the research subjects with a written statement regarding the research. If the researchers fail to adhere to IRB requirements, the IRB has the authority and the responsibility to take appropriate steps, which may include termination of the trial.

An IRB must consist of at least five members with varying backgrounds to promote review of the covered research activities by persons of diverse disciplines. The IRB must have persons qualified in terms of professional experience and expertise. Considerations should be given to cultural, racial, and gender diversity, and sensitivity to such issues as community attitudes. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or physically or mentally disabled persons, the IRB must consider including one or more members primarily concerned with the welfare of those subjects. The IRB must include at least one member whose primary concerns are in scientific areas, one member whose primary concerns are in

non-scientific areas, and one member who is not otherwise affiliated with the institution (one person may fulfill multiple roles). No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

The IRB is required to conduct continuing review of ongoing research at intervals appropriate to the degree of risk, but not less than once per year. It also has the authority to observe or have a third party observe the consent process and the research. IRBs are not required to register with FDA nor inform FDA when they begin reviewing studies.

III. HUMAN SUBJECT PROTECTION ACTIVITIES

FDA, which monitors the activities of research sponsors, researchers, IRBs and others involved in the trial, provides an additional layer of protection. We take no human right more seriously than the protection of people enrolled in clinical trials.

A. FDA's Bioresearch Monitoring Program

In order to protect the rights and welfare of human research subjects and to verify the quality and integrity of data submitted to FDA in support of marketing applications, FDA monitors all aspects of FDA-regulated research through a

comprehensive program of on-site inspections and data audits. FDA uses a combination of surveillance, enforcement, and education to achieve regulatory compliance. Under the Agency's Bioresearch Monitoring Program (BIMO), FDA field investigators and headquarters' scientists conduct site visits of research sponsors, clinical investigators, contract research organizations, IRBs, radioactive drug research committees, and non-clinical (animal) laboratories. In Fiscal Year 1996, FDA conducted approximately 1,070 inspections under the program.[2]

The BIMO program is implemented through several compliance programs: 1) Good Laboratory Practice (GLP) Program (Non-clinical Laboratory); 2) Clinical Investigator Program; 3) Institutional Review Board Program; 4) Sponsor, Contract Research Organization, and Monitoring Program; 5) In Vivo Bioequivalence Program; and, 6) Radioactive Drug Research Committee (RDRC) Program. The Clinical Investigator Program and the IRB Program are the primary programs for ensuring compliance with the informed consent requirements for human subjects in clinical trials.

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[2]Excludes color additives and radioactive drug research committee inspections, and includes domestic and foreign inspections.

FDA's Inspections of Clinical Investigators

Under the Clinical Investigator Program, FDA conducts study-specific inspections and audits of physicians and other investigators conducting clinical trials of FDA-regulated products. In Fiscal Year 1996 FDA conducted approximately 700 clinical investigator inspections.

FDA carries out two principal types of clinical investigator inspections: 1) study-oriented inspections; and 2) investigator-oriented inspections. Study-oriented inspections are conducted on studies that are important to product marketing applications, such as new drug applications (NDAs), product license applications (PLAs) for biological products, and premarket approval applications (PMAs) for medical devices, that are pending before the Agency.

The Agency routinely inspects and audits the pivotal studies upon which the Agency intends to base marketing approval of a new product. In these inspections and audits, FDA examines study records and findings, giving particular attention to protocol adherence and data integrity. We also look for documentation of informed consent and IRB review, approval, and continuing review of ongoing studies.

An investigator-oriented inspection may be initiated as a result of complaints received from subjects about alleged human

subject protection violations or when a study sponsor or FDA staff raise concerns about an investigator. If a clinical investigator fails in his or her obligations, FDA can reject the study, disqualify the clinical investigator from doing additional studies, impose certain restrictions on carrying out future clinical investigations, and in cases of fraud, pursue criminal prosecution. The names of clinical investigators who are disqualified or restricted are publicly available and can be accessed through FDA's home page on the World Wide Web. From 1993 through 1996, FDA disqualified four clinical investigators and imposed restrictions on the investigational drug use of six other clinical investigators.

FDA's Inspections of IRBs

The primary focus of FDA's IRB Program is the protection of the rights and welfare of research subjects, rather than validating the data obtained from research. FDA performs on-site inspections of IRBs that review research involving products that FDA regulates, including IRBs in academic institutions and hospitals as well as those independent from where the research will be conducted. All IRBs regardless of location or affiliation are required to conform to the same regulations and are inspected in accordance with the same compliance program. The inspectional data show that there are similar findings between types of IRBs. It has been demonstrated, however, that

IRBs being reinspected are more often found to be in compliance than those being inspected for the first time.

The frequency of the inspections depends on the performance of the IRB and the number of clinical studies it is monitoring. FDA's approach to these inspections traditionally has emphasized obtaining compliance through education, explanation of requirements, and cooperation but the potential for regulatory or administrative sanctions also is important.

The Agency has a very high standard for the quality of consent forms and applies this stringent standard during its inspections. We look to see whether the consent form includes all the information required by our regulations and whether there are areas in which the consent form could be improved, in our judgment. (We recognize that even a consent form that we find adequate, if submitted to other groups of persons, could be modified to "improve" it further -- so to at least some degree, the review of the adequacy of a consent form is subjective.) One of the reasons why we assign the review of consent documents to IRBs is because the IRB knows the most about its potential subject population and is best able to tailor the consent document to meet the information needs of that subject population.

The most common deficiencies that we find are: 1) lack of clarity about the person to contact if there are questions concerning the research and the research subject's rights in the event of a research related injury; 2) inadequate description of the research procedures to be followed; 3) inadequate description of available compensation if the subject sustains injury as a result of the research; 4) inadequate confidentiality statement; and, 5) inadequate description of alternative procedures that are available to subjects should they choose not to participate in the research.[3] A deficiency in the informed consent document does not necessarily mean that the informed consent process was inadequate. It is the interactive information exchange that is most important to the informed consent process. FDA focuses on the consent form during our inspections because it is the best evidence that we have of the basic information that was exchanged during that process.

FDA can impose administrative sanctions when necessary to protect human subjects of research and in cases of significant non-compliance. Significant non-compliance may include inadequate review of studies, inadequate record-keeping

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[3] FDA recently published a final rule requiring informed consent documents to be dated at the time of signature (61 FR 57278, November 5, 1996). Although a common practice, this was not previously required by regulation. This new rule permits FDA to verify that consent was obtained prior to a subject's entry into a study.

practices that are so deficient that IRB review and approval cannot be verified, or not obtaining adequate informed consent from research subjects. FDA's sanctions include withholding approval of new studies that would be conducted at the institution or reviewed by the IRB, or directing that no new subjects be added to ongoing studies until corrections are made. In the most extreme cases of non-compliance, an IRB may be disqualified from serving as an IRB. Since 1993, approximately 59 warning letters have been issued and several consent agreements have been signed. To date, no IRBs have been formally disqualified by FDA, although several have ceased operations following FDA inspections. FDA also may ask the Department of Justice to initiate appropriate civil or criminal proceedings.

The following is an example of an administrative action FDA has taken with respect to an IRB for noncompliance with the Agency's IRB regulations.

In early 1994, FDA sent a warning letter to a major university, citing failure of the university and its IRB to protect adequately the rights and welfare of subjects in research. In this letter the Agency notified the IRB that it was no longer authorized to approve new studies, [under 21 CFR 56.120(b)(1)], and directed that no new patients be added to ongoing studies, [under 21 CFR 56.120(b)(2)].

The university was instructed to: (1) ensure that the IRB receives and acts on all reports of unexpected adverse events in order to protect adequately the rights and welfare of all research subjects; (2) ensure that the IRB and the principal investigators are informed of their mutual responsibilities for initial and continuing review of IND studies, especially the timely submission and review of all progress reports; and (3) ensure that the informed consent documents meet FDA requirements and that the clinical investigator only uses informed consent documents approved by the IRB.

In March 1994, FDA lifted its restrictions against the University after it agreed to correct the problems the Agency had found and documented the plan to accomplish this objective. At that time, FDA gave the university approval to again approve studies and add new patients to ongoing studies.

B. FDA's Review of Research Conducted Outside of the United States

FDA's protections extend beyond our national borders. All drug, biologic, and medical device studies conducted under an investigational new drug application (IND) or an investigational device application (IDE) are governed by FDA informed consent and IRB requirements. Regardless of the location of the research, our standard is the same.

In general, FDA also accepts foreign safety and efficacy studies that were not conducted under an IND or IDE provided that they are well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community. We recognize that standards for protection of human subjects vary from country to country. If FDA, however, is to accept the data, the conduct of these studies must meet at least minimum standards for assuring human subject protection. Therefore, for studies submitted to FDA which were conducted outside the United States (and not under an IND or IDE), the Agency requires demonstration that such studies conformed with the ethical principles outlined in the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted, whichever provides greater protection of the human subjects.

Thus, as is evident from the foregoing discussion, there are many different entities which must be involved in the protection of human subjects. FDA works hard to make certain that all of the entities understand their roles and responsibilities and that they live up to the expectations placed on them. The protection of the people of this country who are willing to participate in medical research demands no less.

C. FDA's Educational Efforts

On our own and in cooperation with other professional and governmental organizations, we strive to inform those conducting and overseeing clinical research of how to meet their responsibilities and why their doing so effectively is important to protecting the rights and welfare of the human subjects who rely on them.

FDA has developed a set of over two dozen information sheets for IRBs and clinical investigators which address human subject protection issues -- including informed consent -- where questions or problems have arisen over the years. Each information sheet package includes the Belmont Report and the Declaration of Helsinki, important historical documents dealing with informed consent which might not be readily available to users, the FDA informed consent and IRB regulations, and a self-evaluation checklist for IRBs, cross-referenced to the regulations. FDA distributes the information sheets at professional conferences and meetings, through an automated facsimile system, and on FDA's home page on the World Wide Web. More than 6,000 copies have been sent directly to IRBs and to individuals who have requested them.

FDA staff frequently handle calls from IRB staff and members, clinical investigators, regulated industry representatives, and staff of other regulatory agencies on specific problem areas

and to give explanations of particular points in the regulations. When these contacts raise general issues, they are included in new information sheets. FDA also disseminates its educational message through articles and regular columns in professional journals. FDA's publications, including the Medical Bulletin (distributed to health professionals nationwide) and FDA Consumer, also include educational articles on human subject protection issues.

Professional conferences are an important arena for FDA's educational efforts. FDA recently held a one day national conference on human subject protection that was attended by over 500 people affiliated with IRBs, clinical research studies, and other Federal agencies. Additionally, FDA looks for opportunities to magnify the reach and effectiveness of its educational efforts by working with other organizations. For many years, FDA has cooperated with NIH's Office of Protection from Research Risks in a series of several educational conferences annually. The conferences are cosponsored by universities, medical schools, or other nonprofit institutions and are held in different parts of the country. A longstanding collaboration similarly exists with the premier professional organizations in the IRB field -- Public Responsibility in Medicine and Research and the Applied Research Ethics National Association. On a less regular basis, human subject protection education efforts are made at meetings of other health

professional groups and at meetings sponsored by non-profit organizations where sponsors make up a large proportion of the audience.

In addition to their inherent value in focusing attention on the importance of informed consent, FDA's educational efforts support our enforcement and product approval missions. Educated researchers who devote appropriate attention to informed consent and other human subject protections are likely to conduct studies of high quality in other respects as well. Such studies are easier for FDA to review and audit, and approvals can be issued more rapidly. The ultimate beneficiary is the American public, both those who participate as subjects in research and those who are treated with the products approved on the basis of that research.

IV. Interaction Between FDA and Departmental Regulations

Both FDA and the Department of Health and Human Services (HHS) have regulations pertaining to the protection of human subjects (21 Code of Federal Regulation (CFR) Parts 50 and 56 for FDA; 45 CFR Part 46 for HHS). The HHS regulations apply to research that is conducted or supported by HHS[4]; FDA's regulations apply to human subject research involving products regulated by FDA, whether privately or publicly funded. These FDA-regulated

[4]The implementation of these regulations is the esponsibility of the National Institutes of Health (NIH).

products include, for example, investigational drugs, biologics, and medical devices. The FDA and HHS regulations are essentially identical, with differences only where required to reflect the distinct statutory mandate of the organizations and the focus of FDA regulations.

The two agencies apply the regulations in ways fitting their distinct missions. NIH implements the HHS regulations through assurances made by the institutions where the research is conducted. FDA regulates the investigators who conduct the research and the IRBs which review proposed research studies.

If a research project is conducted or supported by HHS and involves a product regulated by FDA, both sets of regulations will apply. In addition, most large research institutions receiving grant and contract support from HHS have agreed to review all research involving human subjects conducted at the institution in accordance with the HHS regulations regardless of the source of the funding for any particular study. The two sets of regulations are complementary and together they set forth criteria that are needed to protect research subjects.

FDA regulates clinical research of investigational drugs, biologics, antibiotics and medical devices under sections 505(i), 507(d) and 520(g) of the FD&C Act. FDA first imposed informed consent requirements on January 8, 1963, pursuant to

the 1962 amendments to the FD&C Act, which required that informed consent be obtained in most, but not all, research involving drugs. Later, in 1976, Congress imposed, through the Medical Device Amendments, an informed consent requirement for research involving medical devices, which was similar, but not identical, to the informed consent requirement for drugs. In 1981, FDA promulgated comprehensive informed consent regulations which applied the most recent statutory requirements to all FDA regulated research (21 CFR Part 50).

In 1981, FDA and HHS simultaneously promulgated new regulations establishing standards governing the composition, operation, and responsibilities of Institutional Review Boards (21 CFR Part 56, for FDA and 45 CFR Part 46, for HHS). These regulations established a common framework for the operations of IRBs that review research funded by HHS and research conducted under FDA regulatory requirements. In 1991, the "common rule" (modeled after the core provisions of the HHS regulations) was adopted by HHS, FDA and 14 other Federal departments and agencies that conducted, supported or regulated research involving human subjects. FDA modified its regulations to conform to the common rule to the extent permitted by its statutes. Last year, FDA published a draft guideline -- "Good Clinical Practice: Consolidated Guideline" under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of

Pharmaceuticals for Human Use (ICH). This guidance, while not a regulation, defines what is good clinical practice and provides a unified international standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

V. LIMITED EXCEPTIONS TO THE INFORMED CONSENT REQUIREMENTS

Having discussed the system for human subject protection, it is important to recognize that there are limited circumstances when informed consent is not obtained from a human subject or his or her representative. There are three "exceptions" to FDA's informed consent requirements. These exceptions are: 1) for a physician to preserve the life of an individual patient; 2) for the conduct of a narrow class of research in emergency settings; and 3) for use by the Department of Defense (DoD) of specific investigational products in combat exigencies.

The FD&C Act specifically requires that investigators inform subjects receiving drugs under an IND that the drugs (and biologics) are investigational and "obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgement, contrary to the best interests of such human beings" (Section 505 and 520). The Medical Device Amendments of 1976 provided that the sponsor of clinical investigations must "assure that informed

consent will be obtained from each human subject (or his representative). . . except where subject to such conditions as the Secretary may prescribe, the investigator conducting or supervising the proposed clinical testing of the device determines in writing that there exists a life-threatening situation involving the human subject. . . which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative" (Section 520(g)(3)(D)). The three exceptions to the informed consent requirements that FDA has promulgated into regulation meet the standards described in those two statutory sections.

A. Preserving the Life of the Patient

According to the first exception (21 CFR 50.23 (a) and (b)) which has been in effect since 1981, informed consent of the subject or his/her legally authorized representative is required unless the investigator and a physician who is not otherwise participating in the clinical investigation, certify in writing, before the test article's use, that:

1. The subject is confronted by a life-threatening situation necessitating the test article's use.
2. Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain

legally effective consent from, the subject (for example, if the subject is unconscious). In contrast, a subject's inability to speak a particular language is not considered an inability to communicate.

3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy provides an equal or greater likelihood of saving the subject's life.

The first three requirements are contained in the Medical Device Amendments. The fourth requirement was added by FDA to prevent routine reliance on the exception.

The regulatory requirement for this exception "applies to individual situations and not to categories of studies as a whole" (46 FR 8945, January 27, 1981), and suggests that there should be great confidence in the effectiveness of product, i.e., the situation must "necessitate" use of the product.

B. Conduct of Research in Emergency Settings

Because the section 50.23 exception was not formulated to apply to clinical trials, in October 1996 FDA promulgated a limited exception to the informed consent requirement to permit the conduct of a narrow class of research involving subjects in life-threatening situations (21 CFR 50.24). These regulations

set forth minimum standards designed to protect individuals who may benefit from emergency research (61 FR 51498, October 2, 1996). At the same time, the Secretary, HHS, announced a comparable waiver of informed consent requirements in certain emergency research subject to the HHS regulations (61 FR 51531, October 2, 1996).

FDA developed this second exception to the informed consent requirements following extensive consultation and deliberation with the ethics and research communities as to whether and how research could be ethically conducted in the acute care/emergency medicine context. In the summer of 1993, the Commissioner of Food and Drugs received letters from the neurology and emergency medicine communities expressing concern about their inability to conduct emergency research in subjects unable to provide informed consent because of conflicting HHS and FDA regulatory requirements. At a May 23, 1994, hearing of the Subcommittee on Regulation, Business Opportunities, and Technology, House Committee on Small Business, problems encountered in securing informed consent of subjects in clinical trials of investigational drugs and medical devices were discussed. At that hearing, Representative Wyden emphasized the need to harmonize the HHS and FDA regulations.

On October 25, 1994, professional and patient organizations and the bioethics community met at the Coalition Conference of

Acute Resuscitation and Critical Care Research to discuss this problem further. Following this conference, the Coalition developed a consensus document to resolve some of the issues concerning informed consent and waiver of consent in emergency research. The issue received further broad discussion at a meeting of the Applied Research Ethics National Association (Boston, MA, October 30, 1994) and at a conference sponsored by Public Responsibility in Medicine and Research (Boston, MA, November 1, 1994).

Concurrently and at the direction of HHS, FDA and NIH were working together to harmonize their respective informed consent regulations as they pertained to this emergency research. On January 9-10, 1995, FDA and NIH cosponsored a Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances in order to obtain as much public input from the research, legal, ethical, and patient advocacy communities as possible. FDA also sent "Dear Colleague" letters to the IRB community, called the major consumer and minority organizations which we thought would be interested in the proposed rule, and held briefings for the emergency research organizations as well as minority organizations in which questions about the rule could be addressed. It was only after all of these activities that FDA published its proposed rule on September 21, 1995 (60 FR 49086).

FDA received 90 comments in response to the proposed rule. The vast majority of these comments supported the proposal, although frequently the comments contained suggestions or requests for clarification. Of the 16 comments opposed to the proposed rule, the majority were from individuals who concluded that informed consent should not be waived under any circumstances. The comments were addressed in the preamble to the final rule published in October 1996.

The final rule provides access to potentially promising experimental treatments to patients in life-threatening situations. This rule sets forth special protections to human subjects who may benefit from this research, but who are not able to give consent on their own, and for whom a family member or legally authorized representative is not available to either withhold or give consent on the subject's behalf. Clearly, any researcher who can obtain informed consent must do so. Frequently, there are ways to design a study so that one is not confronted with emergency situations in which consent cannot be obtained. But in some cases, a subject cannot give his or her informed consent, for example, when there is a life-threatening emergency and there is no one available who is authorized to consent to an experimental treatment that might save that person's life. In that case, the Belmont Report directs us to

protect these individuals with diminished autonomy[5]. That is what the emergency research rule does. It recognizes the need for rigorously designed studies to obtain data on interventions in acutely life-threatening situations such as cardiac arrest and traumatic brain injury in those cases where existing therapies are either unsatisfactory or unproven and consent is not feasible. Without such studies, new therapies for critically injured patients may never be validated and patients in need of emergency medicine may never receive the benefit of improved treatments. Alternatively, such therapies could become widely used in the practice of medicine without any rigorous demonstration of their safety or effectiveness through clinical trials and emergency medicine physicians may never know whether they are in fact saving lives or harming patients through these interventions.

The emergency research regulation requires the following actions to be accomplished. Each study proposing to invoke

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[5]The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research stated in The Belmont Report that: "Respect for persons incorporates at least two basic ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy" (44 FR 23192, April 19, 1979). This report was in response to one of the National Commission's mandates, contained in the "National Research Act", P.L. 93-348 (See 42 U.S.C. 218). That mandate was to identify the basic ethical principles underlying clinical research.

this waiver must be submitted to FDA as a separate and clearly identified investigational device exemption (IDE) application or investigational new drug (IND) application. This will permit the Agency to very carefully review each of these studies to help ensure that they meet the narrow criteria of the rule before the study is allowed to proceed. The IRB and a physician free of conflict-of-interest must ensure each of the following for these emergency research activities to proceed:

- The human subjects are in a life-threatening situation;
- Available treatments are unproven or unsatisfactory; and
- Research is necessary to determine the safety and effectiveness of the particular intervention.
- It is not feasible to obtain informed consent from the subjects as a result of their medical condition or from the subjects' legally authorized representative because the intervention must be administered before they could feasibly be reached, and there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- Participation in the research holds out the prospect of direct benefit to the subjects because: the life-threatening situation necessitates intervention; information from appropriate preclinical (animal) studies and related evidence support the potential for the intervention to be beneficial; and the risks associated with the research are reasonable in light of what is known

about the condition, the risks and the benefits of current therapy, and what is known about the risks and benefits of the proposed intervention.

- The research could not practicably be carried out without the waiver. That is, the research could not practicably be carried out in a subject population who could provide informed consent.
- The protocol must define the length of the potential therapeutic window based on scientific evidence and the researcher must commit to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking that representative for consent rather than proceeding without it. The researcher must summarize his or her efforts and make this information available to the IRB at the time of continuing review. The "therapeutic window" is the period of time in which the patient must receive the therapeutic intervention if it is to be effective.
- The IRB must have reviewed and approved informed consent procedures and an informed consent document consistent with FDA's informed consent provisions (21 CFR 50.25). These are to be used with subjects or their legally authorized representatives in situations where their use is feasible.
- The IRB also must review and approve procedures and information to be used when providing an opportunity for a

family member to object to a subject's participation in the research.

Additional protections of the rights and welfare of subjects are provided in this rule. These additional protections include:

- Consultation with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
- Public disclosure to both of these communities prior to initiation of the research of plans for the research and its risks and expected benefits;
- Disclosure to the public of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; and
- Establishment of an independent data monitoring committee to exercise oversight of the research.

Because the default in this rule is that, once research has been approved by an IRB, eligible subjects are entered into these studies, the rule expands the number of caring individuals who may object to including a subject in one of these studies. Thus, if consent is not feasible from either the subject or a legally authorized representative, the

investigator must commit to attempting to contact within the therapeutic window, the subject's family member (who may not be a legally authorized representative) and asking whether he or she objects to the subject's participation in the research. The investigator's efforts to make this contact must be summarized and made available to the IRB at the time of continuing review.

The IRB also is responsible for ensuring that procedures are in place to inform each subject, legally authorized representative, or family member at the earliest feasible opportunity of the subject's inclusion in the research, the details of the research and other information contained in the consent document, and that they may discontinue further participation of the subject at any time without penalty or loss of benefits to which the subject is otherwise entitled.

These policies establish narrow limits for allowing research without informed consent in certain studies of emergency medical interventions, and harmonize these standards throughout HHS. We believe HHS's new overall approach to emergency research situations may offer the best hope, in an ethical manner, to critically ill, unconscious persons who have no readily available legal representative to give consent and who cannot be successfully treated through conventional means, but might benefit from a promising experimental intervention.

Since the promulgation of the final rule on emergency research, FDA has tracked all INDs and IDEs submitted under this rule. We have committed to an ongoing evaluation of the implementation of this rule to ensure its adequacy for protecting research subjects and to ensure it is appropriately applied. To date, there have been very few submissions under this rule. We have received one IDE application and four IND applications under the emergency research rule. This rule was designed, and is being used, only when it is not feasible to conduct research without a waiver. Thus, this rule is being used as it was designed -- only for that limited class of emergency research which cannot be conducted without a waiver and which meets the stringent criteria built into the rule to protect the research subjects.

This life-threatening situation rule was promulgated in response to growing concern that existing rules were making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized. By permitting certain adequate and well-controlled clinical trials to occur that involve human subjects who are confronted by a life-threatening situation and who also are unable to give informed consent because of their medical condition, the Agency expects the clinical trials to allow individuals in these situations access to potentially life-saving therapies and to result in the

advancement in knowledge and improvement of those therapies used in emergency medical situations that currently have poor clinical outcome.

C. Department of Defense Combat Exigencies

The third exception to our informed consent requirements concerns the use of an investigational drug or biologic in certain situations related to military combat. During the months preceding the Persian Gulf War, DoD had discussions with FDA regarding the potential use of specific investigational products in military personnel serving in the Persian Gulf. We also had extensive internal discussions involving technical and policy-level staff, as well as experts from other Federal agencies and academia. It was thought that the products under discussion represented the best preventive measures for providing protection against possible attack with chemical or biological weapons. DoD requested the assistance of FDA in allowing the use of these products in certain battlefield or combat-related situations in which they considered obtaining informed consent "not feasible." FDA gave considerable deference to DoD's judgment and expertise regarding the feasibility of obtaining informed consent under battlefield conditions.

In response to this request, on December 21, 1990, FDA published an interim regulation amending its informed consent

regulations. This regulation allowed the Commissioner of FDA to determine, upon receipt of an appropriate application from DoD, that obtaining informed consent from military personnel for use of a specific investigational drug or biologic would not be feasible in certain circumstances, and to grant a waiver from the requirement for obtaining such consent.

The exemption extended, on a case-by-case basis, only to investigational drugs (including antibiotic and biological products, including those for protection against chemical and biological warfare agents) for use in a specific military operation involving combat or the immediate threat of combat. A request from DoD for an informed consent waiver must include the justification for the conclusion (made by physicians responsible for the medical care of the military personnel involved) that: 1) the use is required to facilitate the accomplishment of the military mission; 2) the use would preserve the health of the individuals and the safety of other personnel, without regard for any individual's preference for alternate treatment or no treatment; and, 3) the request contains documentation to indicate that the protocol has been reviewed and approved by a duly constituted IRB for the use of the investigational drug without informed consent.

Each application for waiver from the informed consent requirements was assessed by the appropriate FDA review

division, and by the Agency's Informed Consent Waiver Review Group (ICWRG). The ICWRG included senior management of the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Office of General Counsel, the Office of Health Affairs, and NIH's Office of Protection from Research Risks. The ICWRG core was supplemented by technical experts as appropriate for the particular investigational drug being considered for exception. The ICWRG considered DoD's justification supporting the request for the waiver and the reviewing division's evaluation of the available safety and efficacy data. The ICWRG requested additional supporting information in some cases, and required changes in the information to be provided to the troops in several rounds of iterative exchanges with DoD. The ICWRG then made a recommendation to the Commissioner regarding whether or not to grant the waiver. The Commissioner made a decision on the application and informed DoD in writing.

Under this regulation, waivers were granted for two products during Operation Desert Storm/Shield--pyridostigmine bromide and botulinum toxoid vaccine. Although FDA had concluded that informed consent was not feasible, FDA did obtain DoD's agreement to provide accurate, fair, and balanced information to those who would receive the investigational products. To do this, DoD developed information leaflets on both products with FDA's input and these leaflets received final FDA approval.

Following the cessation of combat activities, the Assistant Secretary of Defense for Health Affairs notified the Commissioner in a March 1991 letter that DoD considered the two waivers granted under the interim rule to be no longer in effect. He also informed the Commissioner that DoD had ultimately decided to administer the botulinum toxoid vaccine on a voluntary basis.

Since that time, the Presidential Advisory Committee on Gulf War Veterans' Illnesses has recommended that we "solicit timely public and expert comment on any rule that permits waiver of informed consent for use of investigational products in military exigencies." (Final Report, page 52.) FDA has carefully evaluated the committee's recommendations as well as other information that has come to its attention. FDA has engaged in discussions within the Agency, with DoD, and with others on this important topic. As a result of these discussions, the Agency will solicit public comment in line with the committee's report. This public comment will be directed towards whether the FDA should finalize the interim rule, modify it, or eliminate it completely.

VI. CONCLUSION

The first layer of the subjects' protection is provided by the medical research sponsor. It is the responsibility of the sponsor to design the research study to be ethically and

scientifically sound, select qualified researchers, provide them with the information they need to properly conduct the research study, and ensure proper monitoring of the study. The second layer of protection is provided by the researcher, whose professional and civic obligation is to conduct ethical research and make sure that the study participants are apprised of, and fully understand, the potential risks and benefits of the research. The third layer of protection is provided by IRBs. It is the responsibility of the IRBs to develop and follow procedures for initial and continuing review of the integrity of the research and the protection of the rights and welfare of its human subjects. The last layer of protection is provided by FDA, which regulates the organization and procedures of IRBs, researchers, research sponsors, and others involved in clinical trials. These layers of protections are applied to each clinical study to ensure the integrity of the data and in order to protect the rights and welfare of the human subjects of clinical research.

We take very seriously our obligation to protect the rights and welfare of all research subjects who participate in research involving FDA-regulated products. We believe that our regulations and inspection programs are important to help ensure that human research subjects are protected at the same time that vital information on the safety and effectiveness of drugs, biologics, antibiotics, and devices is gathered.

I would be happy to answer any questions you have about FDA's oversight and regulation of research activities.

Dr. FRIEDMAN. Thank you for the opportunity for the statement, sir.

Mr. BURTON. First of all, let me thank you and your staff for being with us today. I know it's an imposition, but we think it's important that we discuss these issues. The reason that we went into the fenfluramine issue was because it became so prominent in the news in just the last few days and we thought that it was something that was relevant to what we've been concerned about and that is the health of people and how the FDA works. So we thought we would add that to the agenda today. We think your agency was given adequate time. I hope, if there was a disagreement, I apologize for that but we thought we had adequate time to prepare for this and the minority was made aware of it last Friday.

Let me ask you a couple of questions about that fenfluramine situation. You had children in New York City in the inner city, that were subjects of this experimental procedure and even after it became apparent that this caused health problems in adults, it was allowed to continue to be used and injected into children from the inner city there. Why was that?

Dr. FRIEDMAN. Well, sir, I don't know when that particular question was addressed to the agency. I only found out about it this morning. So I can assure you that we can provide a much more substantive answer with more time. But I'm happy to share with you the information I have today.

Mr. BURTON. What we have here, as reported in the newspaper—and I don't always believe what the newspapers say, but—is a Robert Temple in your agency?

Dr. FRIEDMAN. Yes.

Mr. BURTON. He is alleged to have said, quoted as saying, "Just because a drug is pulled off the market . . . it still may have a legitimate use for research. The benefit of the product will outweigh the risk. Lumpkin and Dr. Temple, the director of the FDA's Office of Drug Evaluation, admitted they had 'very little data' showing the impact good or bad one or two doses of fenfluramine will have on children." I don't understand that——

Dr. FRIEDMAN. Well, let—if I may, I'll be happy to respond, sir. Again——

Mr. BURTON. Your—he'd be—I'd be happy to hear his response as well.

Dr. FRIEDMAN. And—as I would be happy to offer it, sir. I think the critical issues here, have to do with the question of whether or not the perceived benefits of the investigation are relevant. I understand—and I've just received information on this this morning so my information is not totally complete in this regard—that when this product was removed from the market, those investigators who were using it were contacted and told of this information. Now it is absolutely correct that there are some products which, when they are removed from the market for one indication, continue to be researched for others and there are some examples of great benefit coming from such situations.

Mr. BURTON. What—but doctor, there were heart valve problems created——

Dr. FRIEDMAN. May I continue please, sir?

Mr. BURTON. Sure.

Dr. FRIEDMAN. Thank you. What was asked at the time of the product being removed from the market is that all clinical trials cease and that if an investigator wished to continue the research, that certain things must be done. First and most importantly, there must be adequate informed consent. And the informed consent in this process, the document itself was modified. You mention that there were some children involved. There were also, as I understand it, more adults than children, but there were a number of individuals involved. Those people had a new informed consent document that talked about the risk of heart disease. That's No. 1. No. 2, those people who wished to participate in this clinical trial, and it was voluntary, underwent a cardiac examination to examine their heart valves to see if there was any damage there before they began taking the one dose that they would be offered. Afterwards they had to submit to a second heart valve examination. It's not painful, but it is a highly sophisticated test. Third, the local investigational review board, the board that knows best the local situation of the people involved, the investigators who are doing the research, had to be informed and had to agree that this was an appropriate technique.

You raise issues about informed consent and how this process is best conducted. As I'm sure you recognize, sir, there are at least three important components here, one of which is the Food and Drug Administration, but IRBs, the Institutional Review Boards that are critically involved in this unfortunately aren't going to be represented here today. I think that's lamentable because they've a very important role to play. Nor the Office for Protection of Research Risks, OPRR.

Informed consent was provided. All appropriate testing was done. This was clearly a voluntary kind of activity. And we take very seriously the special care that must be given to populations of patients whether they be children, patients who are desperately ill, patients with psychiatric conditions, and so forth. That there must be built in extra safeguards for those individuals because they by themselves can't look after their own best well-being.

Mr. BURTON. I understand. But we're talking about children. There may be some adults, but we're talking primarily about children who would not be able to give informed consent. Their parents could. But Dr. Temple said very little data exists on this and so how did you know that children would not be affected down the road after being subjected to this treatment?

Dr. FRIEDMAN. There are many thousands of patients who've been treated with this product.

Mr. BURTON. Children?

Dr. FRIEDMAN. No, adults. Before research is carried out in children, frequently there must be a large experience in adults. Not always, but frequently that is the case. This is a situation where not just the Food and Drug Administration, but a body of scientists and the Institutional Review Board looking at this information believe that there was a real promise of scientific information being gained that might be of help to these children and adults later. I can——

Mr. BURTON. But the children—but, Doctor, you already knew that there had been some heart valve problems created by the use of this drug in the past.

Dr. FRIEDMAN. We have never seen—there has never been reported a case of any heart valve or other illness from taking—a heart valve or blood vessel illness, I should say, from taking one dose. That's not been reported to the agency in thousands of patients who've been treated in adults or anyone else.

Mr. BURTON. But how did you know? You know, children are much smaller than adults. How did you know that——

Dr. FRIEDMAN. That's very appropriate, sir.

Mr. BURTON. How did you not know—how did you know that it would not adversely affect a child because the dose might—because they're much smaller, might have a much greater impact on their bodies than it would with an adult in the same amount.

Dr. FRIEDMAN. The fact that there are unknowns in clinical research is certainly true. But I know, sir, because you've been passionately eloquent about this, the need for investigation under properly controlled situations is something that you have been an ardent spokesman for.

Mr. BURTON. Right.

Dr. FRIEDMAN. I think that this is a situation where if you say that the Food and Drug Administration must only allow that research to go forward for which the answer is almost surely known, we would restrict medical research and I know you don't want that, nor do I.

Mr. BURTON. No, I want to—I don't want to——

Dr. FRIEDMAN. I certainly don't—I'm sure you don't mean that.

Mr. BURTON. No, what I wanted to understand, at least in part in this hearing today, is why when there was a substance that had damaged adults that it was continuing to be used in the scientific research program on children after the fact. And the answer that was given to the newspapers by Dr. Temple did not seem adequate to me. And all I want to find out for sure is why. Obviously research is important.

Dr. FRIEDMAN. Well, let me just say one other thing and then I'm more than happy to have Dr. Temple join me to respond specifically in case that quotation wasn't thoroughly complete or entirely adequate. I'm very happy to have him join me. The thing I have to reaffirm, though, sir, is that the risks to adults was described in detail in the informed consent process that the parents of these children or that the adults had to sign. That was disclosed in there. I looked at the informed consent document this morning myself to assure myself of the fact that that had not been left out.

Now you and I might say that, for us as individuals, we have a threshold for what clinical trials we would participate in or allow our children to. And that's certainly our privilege. But I believe that the critical question here—I think this is question of personal choice as well. And I know that you've been very keen and very supportive of having patients have their choices. What you've required and what I thoroughly support with you, sir, is having the proper information disclosed to that individual in a noncoercive and in a thoroughly educational mode. That's extremely difficult. I do recognize that and I'm not making light of that.

Nonetheless, I believe that our primary responsibility is to provide the information, to make sure that things are ethically conducted. If a patient or if a parent wishes to have, with the child's assent, our agency recommendation to participate in such a study they should do so fully knowledgeable of all the side effects that we're aware of.

I'm sorry to have gone on so long. Dr. Temple might want to embellish on his comment.

Mr. WAXMAN. Excuse me, Dr. Temple, I have to leave and——

Dr. FRIEDMAN. I'm sorry, sir.

Mr. WAXMAN [continuing]. If the chairman would permit me. You can go in the second round.

Mr. BURTON. We'll defer and let him answer.

Dr. FRIEDMAN. Thank you. Please go right ahead.

Mr. WAXMAN. It's my 5 minutes of questions to you.

Dr. FRIEDMAN. Yes, sir.

Mr. WAXMAN. We had two hearings in this committee on a different subject and we were only informed as the chairman indicated Friday, that we now have a different subject for today's hearing. Well, I'm going to have written questions to you for the record——

Dr. FRIEDMAN. Yes, sir.

Mr. WAXMAN [continuing]. To explore both areas. But on this particular issue, thalidomide comes to mind. That was a drug that was pulled off the market and now it's part of a research protocol. Tell us about that and is there anything wrong with using that research?

Dr. FRIEDMAN. I think it's a very important example. As we all know, thalidomide had horrible side effects as a sleeping agent. It did result in sleep, but it had terrible effects on developing fetuses. The drug was not on the market in the United States, thankfully, but it continued to be tested in the United States because it had a very powerful and positive impact on patients with a certain very painful form of leprosy. Now this was such a terrific treatment. It was so valuable for these patients that we continued to allow its use under very carefully controlled conditions where you did worry about the possibility of pregnancy, but did everything you could to prevent that. In fact, we have recently reviewed and approved an application for thalidomide under those very same circumstances.

Mr. WAXMAN. So the research on thalidomide is a different ex——

Dr. FRIEDMAN. It's an excellent example.

Mr. WAXMAN. It's a different kind of research.

Dr. FRIEDMAN. That's right.

Mr. WAXMAN. On the use of the drug when it was available, not in the United States, but in other countries.

Dr. FRIEDMAN. And the information that was supplied to patients receiving that information for that medication was as fully informative as what we've just described for fenfluramine. As you recognize, sir, I'm not defending the experiment with fenfluramine or criticizing it. I don't know whether it's going to be a positive piece of scientific information, that we will learn important new insights, but I do believe that it is appropriate and ethical and that it's being conducted under carefully scrutinized circumstances.

Mr. WAXMAN. Now both the FDA, which you represent, and Dr. Varmus, who's the head of the National Institutes of Health, testified extensively last year at our subcommittee hearing chaired by Mr. Shays on this issue of informed consent and I think this hearings focus on FDA is somewhat misleading, sort of like a blind man trying to describe an elephant simply by looking at the trunk. Isn't it true that the oversight of human research is a responsibility of thousands of Institutional Review Boards, trial sponsors, the NIH Office of Protection Research Risks, the FDA, and, ultimately, the scientists who conduct the research in accordance with professional standards?

Dr. FRIEDMAN. That's exactly right. And some people say it's the very complexity and multiple nature of that system that builds in special protections for patients, that those number of different perspectives are very important in protecting patient rights. At any point there may be a difficulty. There may be an investigator who doesn't follow the rules or an IRB that doesn't function as well as it should. We recognize that there can be problems at any point in the system, but I think that collectively we are all committed to having an ethical, proper system.

Mr. WAXMAN. For this hearing, the only one as I can tell, that's being asked to respond to the concerns that are legitimately being raised about clinical trials and adequacy of informed consent, the placebo trials, is the FDA.

Dr. FRIEDMAN. Lamentably, that's true.

Mr. WAXMAN. And others are involved as well.

Dr. FRIEDMAN. That's very true, sir.

Mr. WAXMAN. Now, as an accomplished medical researcher and as acting commissioner, can you explain to us the purpose of a placebo-controlled trial? When is a placebo necessary and are there situations where a placebo group is simply inappropriate?

Dr. FRIEDMAN. If I may, let me begin with the third of your questions, because in some sense it's the most important. There are clearly a number of situations where a placebo-controlled trial is inappropriate and is not ethical and we don't sanction or approve such trials. It's absolutely true. It's especially true if there is effective treatment, life-saving treatment, dramatically beneficial treatment that's available. We feel very strongly that under those circumstances patients should not be denied those options.

Clinical trials are very complicated and trying to decide how best to show the benefit of a new treatment can be very difficult. We believe that the principles that need to be adhered to are, first of all, complete informed consent. So when a placebo is used, a patient is fully informed about that and he or she makes the choice. There've been some dramatically effective and dramatically startling trials recently. Just last week, the announcement about the tamoxifen trial for breast cancer prevention—what I think of as a major important trial—that was a placebo-controlled trial. It was scrutinized very carefully by hundreds of investigators, thousands of patients participated, dozens or more review boards. Under those circumstances, it was a—it was the proper choice to make, we believe. It demonstrated a new therapy that—it has promise for many, many patients.

Distinguished scientists will have legitimately different points of view about when a placebo-controlled trial is appropriate and when some other kind of trial is not appropriate. I think that specifics must be tailored to the disease, to the options that exist for the patient, for the condition of the patient, and, most of all, for the patient's choice. There are some situations in which we believe that placebo-controlled trials are appropriate. There are other situations where you think they are entirely inappropriate. But we think that the seriousness of the condition, the relevance of other options, it might have real patient benefits, and patient preference are some of the most important features.

Mr. WAXMAN. Are all these decisions FDA decisions?

Dr. FRIEDMAN. No, sir. We certainly have a role and we certainly want to help with this, but these are decisions that are made at the investigator level; at the IRB level; at the sponsor of the product level; if there's a NIH-sponsored trial, at their level. We participate in this colloquium, but we're only one of several participants.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. BURTON. Mr. Horn.

Mr. HORN. Thank you very much, Mr. Chairman. Let me review some of the matters. What year was the first time the FDA knew of this experiment by the New York State Psychiatric Institute?

Dr. FRIEDMAN. Sir, I would have to provide that for the record. Again, I was not informed that that——

Mr. HORN. You don't have the file or papers on you?

Dr. FRIEDMAN. No, sir, not with me, no, sir. I'm sorry.

Mr. HORN. Who in the FDA has such a file?

Dr. FRIEDMAN. The appropriate portion of the Center for Drug Evaluation and Research, sir.

Mr. HORN. And they didn't give this to you to prepare for this hearing?

Dr. FRIEDMAN. No, sir, I found out about this, this morning at 9 that this would be part of the hearing. I'm sorry, sir. I don't want to waste your time. I would have much preferred to prepare properly for this issue. This was not an issue that we had been inform—that I had been informed about nor do I know of anyone else on my staff who passed that information on to me.

Mr. HORN. Well, my question, obviously, gets nullified by not being prepared and the question is—let's then put it on a hypothetical. Let's say the experiment started in the 1980's and it's now the end of the 1990's. What's the policy of the FDA in reviewing the consent papers on projects that come to you for approval? How often do you review them to see that they're conforming to the consent? And, No. 2, to see what, if any, change has occurred in the protocol with regard to the pharmaceuticals that are being tested?

Dr. FRIEDMAN. I would ask Dr. Nightingale if he would please assist me with this answer. We certainly—we rely upon the Institutional Review Board to assure that proper informed consent documentation and informed consent occurs. We site visit those IRBs on a regular but episodic basis and look at those forms at that time. It is not a mandatory requirement that we review all consent forms for all situations when the project is first started. Frequently, if not always, the sponsor supplies that to us for their—for our review at the time of initiation. We make efforts, and certainly did in this

case I know because I received this fax this morning, to update informed consent documents to require that these be updated so that patients will be given the latest information when it becomes available.

I can speak to you from other venues not about this case, but as you've pointed out, the hypothetical case. When I was a clinical investigator at a university and then when I was at the National Cancer Institute, I had to both serve on Institutional Review Boards and present before them proposals that they would review. And whenever I found out new information as an investigator, I modified my consent form, I took it back to the IRB. Often they wouldn't require to meet with me; they just took that as a paper submission, but on occasion they would. But when I was at the National Cancer Institute and we were sponsors of some trials, we certainly asked for informed consent documents to be updated and changed as new information emerged about a side effect that had not previously been noted or, in some instances, a benefit that wasn't known before.

I don't know if Dr. Nightingale wants to add anything.

Dr. NIGHTINGALE. Right. May I just add a little to that. Basically, the FDA does the review of informed consent in a variable manner. Certain parts of the agency routinely do review informed consents; others don't. It depends on the situation as well as the product class. When there are deficiencies found, when FDA does a review itself, they are passed on to the sponsor and changes are made throughout the system.

But, more typically, where the rubber meets the road, of course, is at the IRB, as Dr. Friedman has stated before. That is the main locus for this ethical review and any changes that are made there must be made before a trial can begin. And that's where this is done.

Mr. HORN. What is the FDA policy if there's an introduction of a new drug that hasn't been in the original protocol? Do you then go back to get informed consent? Or how do you handle that? How do you require that——

Dr. FRIEDMAN. I want to make sure I understand your question.

Mr. HORN. Well, I'm trying to get at just how vigilant is the FDA in reviewing what an Institutional Review Board has done when there are changes in the protocol? Do you demand that they go back to a new consent on the part of the people that are exposed to that particular experiment? How does that work?

Dr. FRIEDMAN. I think I understand your question. If I don't get it right, give me another chance and I'll try to answer your question again. If you're saying for those people who are currently on a clinical trial, they've agreed to participate, they're enrolled in the study, they're taking the treatment, and then a new observation is found and the consent form is changed. Did those people then get the new information about that consent form? That new observation?

Mr. HORN. Right.

Dr. FRIEDMAN. It certainly would be, depending upon the seriousness of the side effect or the opportunity for providing this information, I think it would be absolutely optimal to do that. I can tell you that my experience at the National Cancer Institute was ex-

actly that, that when we found new information for patients who were receiving the treatment, there were occasions when we had the investigator go back and talk to every patient who'd been recruited to that clinical trial to say to them, here's new information we just want to let you know this for your interest.

You recognize, I know, that at any point in the clinical trial, the patient is given the opportunity to stop, to withdraw from the trial and the consent form must say with no prejudice, with no risk of any adverse health consequences, that they won't be cared for or they'll have to find a new doctor, or anything else. That you promise them that you will care for the patient whether or not they participate in the trial or you will see that they get care whether or not they're in the trial. That always exists for the patients.

Now, I think that the local IRB has the formidable task of reviewing that information. And the GAO report that the chairman referred to earlier points out that IRBs often do a very good job of this. But as this report points out, there are real strains on the system at the OPRR level, at the IRB level, at the investigator level, and that the FDA has strains. But that they recognize that, in general, the system works well, but should work better and is exposed to risks in the future.

Mr. HORN. Because when we talk about the IRB, the Institutional Review Board, has the FDA examined the one that relates to the New York State Psychiatric Institute to see if there are conflicts of interest? I mean, let's face it, I've been a dean of research in my past incarnations and you can easily have conflicts of interests of other faculty and it's each one scratch each other's back type of arrangement. What's the FDA done in this case to look at the situation in terms of the makeup of that board? And my next question's going to relate to informed consent for children. But let's deal with that.

Dr. FRIEDMAN. Let me answer—if I may, I'll respond subsequent to the hearing since I don't have that information. We will identify for you when last that IRB was site-visited, what was found at that time. Again, I don't have that information. I would have—I'm as dissatisfied with this as you are, sir. It's my intention to be here to engage in the highest quality discussion that we can and I'm frustrated by not having adequate time and adequate notice to prepare for this and I apologize to you, sir.

Mr. HORN. Well, I appreciate that. But now on the general policy of informed consent of children, what are the FDA rules on that?

Dr. FRIEDMAN. Again, I'll have Dr. Nightingale supplement my answer. The short answer is that the parent or legal guardian must provide his or her consent. But our agency policy is one step further than that which is that the assent of the child is something to be striven for as well. Because it's not merely that children are totally passive in this as all of us as parents clearly recognize in good ways and in times of illness. Nonetheless, we want to have the patient's best interests, in this case the children's best interests, looked after by those people who have the greatest care and the greatest knowledge about them. Perhaps Dr. Nightingale can expand.

Dr. NIGHTINGALE. Just to add to that, there aren't specific additional FDA regulations for children in the informed consent area,

but clearly to have the informed consent requirement carried out properly, great attention has to be paid to vulnerable subjects such as children. There is a requirement in the IRB regulations that when you're dealing with vulnerable subjects on a regular basis that the makeup of the IRB should be paid attention to and that you should have those concerned about the welfare of that particular vulnerable group serve on the IRB to assist in the review.

Mr. HORN. Now is vulnerability decided by what age they are? Or is it decided by what psychological and physical condition they're in?

Dr. FRIEDMAN. Well, I would say both are important factors, sir.

Mr. HORN. But what is the age minimum now at which a child can give consent?

Dr. FRIEDMAN. There's an emancipated——

Dr. NIGHTINGALE. I think it varies State to State in terms of the specifics.

Mr. HORN. So FDA follows the State rule, not a national standard.

Dr. FRIEDMAN. If necessary, we'll get back on that.

Dr. NIGHTINGALE. We can check, sure.

Mr. HORN. Well, does anybody of the eight who took the oath know the answer to that question?

Ms. MALONEY. My name is Diane Maloney in the Office of the Chief Counsel and, with regard to informed consent, the informed consent is by the subject or the legally authorized representative and that is determined by State law. So the age, I believe, would be, if the State law is a person is eligible to give consent at 18 in one State, then that would be acceptable. If it were higher or lower in another State, that, I believe, would be what the law would provide.

Mr. HORN. I'm fascinated because, with all the thousands of pages of regulations this Government has turned out since FDA was established under Theodore Roosevelt, I would have thought there'd have been a standard age of consent on a federally approved project across the country.

Mr. COX. Will the gentleman yield?

Mr. HORN. Yes, I'd be glad to.

Mr. BURTON. In fact, why don't we let Representative Cox have his 5 minutes, then we'll come back to you, Mr. Horn.

Mr. COX. Well, I don't mean to interrupt this very profitable line of questioning, I just asked the gentleman from California to yield for a moment.

Mr. BURTON. OK. All right.

Mr. HORN. And I am glad, Mr. Chairman, to yield because I'm due in another hearing right now.

Mr. COX. Dr. Friedman, you said that it was FDA policy, in addition to gaining the legal consent of the parent, also to strive for the assent of the child. What is FDA's policy on that? How old must a child be to give his or her assent?

Dr. FRIEDMAN. I don't know that there's a written policy. I'll have to look into that and supply that to you if I may. I would say that, as a parent and as a physician, I would hope that at whatever age the child was capable of doing it. Obviously, the exigencies of ill-

ness and the frightening situation of a medical facility would make that difficult, but, wherever possible, I think it's ideal.

Mr. COX. Mr. Chairman, who has the time?

Dr. FRIEDMAN. It is, I'm told, sir, that it's in our good clinical practices guidelines and we'll be happy to supply that to you.

Mr. COX. Mr. Chairman, it's my understanding that that's actually what this hearing's about, so I don't think that these questions are off-base at all, and I'm just surprised that the witnesses aren't prepared to answer them, but I do appreciate that you could provide us supplemental information.

Dr. FRIEDMAN. Yes, may I speak to that, sir?

Mr. BURTON. If the gentleman yields briefly, as I understand it, Dr. Temple of the FDA was made aware of this yesterday afternoon about 3 o'clock, when he was contacted by a reporter so that was when everybody at the FDA had their antennae go up. And I would have thought that possibly you could have brought some of those records in that period of time. But, nevertheless, it was very short notice.

Dr. FRIEDMAN. Sir, I think that for a hearing of this importance and for subjects this complex and asking us to deal with all informed consent, all human protection, all access issues, I think that less than 24 hours notice is very difficult. I take this very seriously. I apologize to the committee, but we were not even given formal notification by anybody on the committee that this would be an issue. A reporter calling us is hardly notification from such an important and distinguished committee.

Mr. BURTON. Well, Doctor, let me just say the reason we decided to go into this subject—if the gentleman will yield a little bit further—was because we had the hearing scheduled. It was a timely issue. We apologize for the shortness of notification but we would have had to have you come back at another time and drag all your staff back and we thought that we would try to kill two birds with one stone. So that's the reason for it. Thank you for being here.

Dr. FRIEDMAN. Well, and we're happy to try to respond to it; it's just that I'm—I apologize and I don't wish to be held to not being ready for everything since there was relatively little time. But, Mr. Cox, I'm sorry, I interrupted you, sir.

Mr. COX. That actually amply answers my question and I did not know of the foreshortened notice that you had, and so your answer under the circumstances is quite acceptable.

Dr. FRIEDMAN. But we will respond fully to any questions that you have.

Mr. COX. Just to lay the foundation then, so we're all operating under the same set of assumptions for any questions that I might put beyond that, I take it that you have had an opportunity to review the General Accounting Office report that is titled, "Scientific Research Continued Vigilance Critical to Protecting Human Subjects?"

Dr. FRIEDMAN. Yes, sir. Yes, sir.

Mr. COX. And that you had a chance to lay your hands on and review it even before learning about the hearing today?

Dr. FRIEDMAN. I had looked at it previously but, certainly, this hearing has focused my attention on it, yes, sir.

Mr. COX. And did FDA cooperate with GAO in any fashion prior to their conclusion of their report?

Dr. FRIEDMAN. I don't know the answer to that question. I believe that our general posture is to be very cooperative with GAO.

Mr. COX. It would be my assumption that FDA would——

Dr. FRIEDMAN. There may be something specific about this, but my understanding is in general we work collegially with them.

Mr. COX. So if I approach further questions from the standpoint of this report, with which FDA has been involved, I hope that—and I take it I'm using up all my time in the preamble to the question in any case, I notice the amber light has just turned on—let me get immediately to a question.

Dr. FRIEDMAN. Please.

Mr. COX. To followup on what my colleague from California, Mr. Horn, was just talking to you about, obviously gaining the consent of an adult is one thing and dealing with a human subject that is below the age of majority is quite another. Furthermore, there's an issue when parents give consent for children that doesn't exist when a human being gives consent for himself or herself, because they're separate people and, as much as parents care for children, it's just a different issue.

Specifically, for example, in one of the cases that's resulted in a lot of negative press for the FDA, a young girl was given these experimental doses; she was promised psychological help, and apparently that psychological help was not forthcoming, but, generally speaking, there was consideration for her participation in the test.

What is FDA's general practice when it comes to offering consideration for a child's participation in the test? Can—to use a stark example—can somebody under a protocol approved by FDA—has this ever happened before—give money to the parents if their children are subjected to experimental drugs?

Dr. FRIEDMAN. I don't know the answer to that question. Again, I would have to try and supply that for the record later. I think that the local considerations are some of the most important, and that's why I get back to the absolute central nature of the IRB; the integrity, as Representative Horn described; the non-biased approach; the lack of conflicts of interest. In many ways, the local Investigational Review Board and the local researcher are critical on this issue. I don't know the answer to whether money has ever been given as a consideration for participation in a local trial.

I can—currently, I can tell you that when I was a medical student, I participated in such studies for such reimbursement——

Mr. COX. As an adult.

Dr. FRIEDMAN. As an adult, yes, sir. But not as——

Mr. COX. Not to help somebody else when you were being paid so that they would take a drug.

Dr. FRIEDMAN. Right. I can't—no, sir, and I can't say anything about children.

Mr. BURTON. If the gentleman would yield, let me say briefly, I've been informed that each time a child was injected the parent got $125. Is that correct? It's been reported that they were paid $125 each time there was an injection, which might have been an inducement for a parent to continue in that program. Do you have any knowledge of that?

Dr. FRIEDMAN. I don't, sir. Again, I'll have to look at the record and we can supply that answer later.

Mr. BURTON. OK. Let me just ask, if it's all right, just one or two quick questions, and I'll yield to Mr. Cummings in just a second here. The consent form that you're talking about, after it was taken off the market for adults and the program continued for children, was the consent form changed or was a new consent form required of the children who were in the program?

Dr. FRIEDMAN. I'm not sure I understand the distinction between changed and a new consent form required. New information was required to be added. That new information was added.

Mr. BURTON. And the parents were informed that there was heart damage or suspected heart damage in people who were adults who were taking it? And they continued to keep their child in it after they were informed of that?

Dr. FRIEDMAN. My understanding, sir—and again I apologize; we're spending a lot of time on something that I am absolutely ill-prepared to deal with. My understanding is that these children and these adults only received one or at most two doses. There was no continuing therapy. That's my understanding.

Mr. BURTON. Well, if you could, for the record, if you could get that information to us, we'd certainly like to review it.

Dr. FRIEDMAN. Certainly. And you may well have questions about the questions that——

Mr. BURTON. OK.

Dr. FRIEDMAN. Any questions that you have, we will supply the answers to.

Mr. BURTON. OK. Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

Dr. Friedman, I want to thank you for being here today. I don't think that you owe us any apologies. None. We didn't even know on this side that the hearing subject matter had been changed until this morning. As a lawyer of 22 years, I can tell you that I don't care how prepared I was for a hearing, if somebody changed it in a short period of time, it would be impossible for me to address probably some simple issues, let alone complex issues. And so you don't have to sit there and apologize. There's no one in this room, no one, even up here, who could handle complicated issues on less than 24 hours notice that—and when they got the information from a reporter. And I think that is blatantly unfair to you.

A lot of allegations are being made. You're not in a position—and I understand you got a lot to deal with. You've got a big agency and common sense—and I don't think the American people—I hope they watch this because they will understand; they wouldn't want to be in the position that you're in, and so I—you don't have to apologize to us.

Dr. FRIEDMAN. Thank you, sir. I appreciate that.

Mr. CUMMINGS. You really don't.

Let me ask you some questions that—and our staff prepared for the hearing that you came here for and they spent many, many hours, and I want to thank them and I know they must feel kind of bad because they spent so many hours preparing for the hearing that we were supposed to have. So I need to get back to some of

those things, because I'm interested in them. And I've spent quite a few hours preparing myself.

This is our third full committee hearing on FDA issues. In the first two hearings, some serious charges involving patient access to unapproved therapies were made against the FDA. Given privacy concerns, I want to give you an opportunity to respond as fully as possible. Several witnesses testified to the safety and efficacy of Dr. Burzynski's treatments. Are you familiar?

Dr. FRIEDMAN. Yes, sir, I am.

Mr. CUMMINGS. Do you have any information about the toxicity or the effectiveness of any of Dr. Burzynski's treatments?

Dr. FRIEDMAN. Yes, sir. As you know and as was described to this committee previously, there are a large number of clinical trials currently being conducted by Dr. Burzynski. We fully support the conduct of those clinical trials, because we believe that's the way we'll get answers and that's very important. Dr. Burzynski has recently supplied to us—and these are his data that I'm discussing—information about 828 patients that have been treated with the intravenous form of his therapy; 404 patients were treated on protocols and 424 patients were treated as special exceptions, the compassionate patients that you've heard about in the past.

The benefits that have been seen in these patients have been in some categories not observable. So that, for example, no patient with breast cancer that he reported to us benefited, responded, 0 out of 74; 0 out of 88 lung cancer patients; 0 out of 29 prostate cancer patients. There were other categories where patients did not respond. There were, however, some instances where patients did have a response, albeit at a low range. But we certainly want those clinical trials to continue. Under no observable areas did we see, overall, more than 8 percent of patients having even a temporary benefit.

There were toxicities associated with this treatment. More than half the patients had a significant elevation in their serum sodium; that's the amount of salt that's in your blood. That's kept in very fine balance usually. In more than half the patients, there was a greater than 10 percent increase in the serum sodium level. In some patients it was much higher. We believe that there were serious side effects from those situations.

All told, we have information that is developing for Dr. Burzynski. We want to encourage him to continue the clinical trials to assess this information because it appears that in some categories no benefits are seen, in other categories it must yet be determined.

Mr. CUMMINGS. You mentioned prostate cancer. I think in one of those you said 0 out of 80 I think——

Dr. FRIEDMAN. Twenty-nine patients is what's reported to us recently, yes, sir.

Mr. CUMMINGS. OK. It's just—I just want you to understand that that is a major concern. That's why, I mean, I'm concerned very much. In my district, African American men are dying—I'm not talking about just suffering with it—at alarming rates. And, of course, we're very, very fortunate in my district in Baltimore to have Johns Hopkins there. And we have, of course, Dr. Walsh——

Dr. FRIEDMAN. That's right.

Mr. CUMMINGS [continuing]. Who is one of the greatest physicians in this area operating on folks and treating folks from all over the world, every day. But with—our African American men are dying, and so I just wanted to express my concern. I want to make sure that that issue is addressed. The President has made some statements about it saying that he thinks we need to do a little bit more about it, and I agree, and I just want to put that on the record. Thank you, Mr. Chairman.

Dr. FRIEDMAN. Yes, sir. Yes, sir.

Mr. BURTON. Doctor, I think, since we have two other panels, we might hold you in abeyance, since you've agreed to stick around for a little while, so you could hear what the other people have to testify. So we could ask questions after they've concluded. So we'll excuse you now and ask Dr. Judith Vukov, Joe Foster, and Barbara Foster to approach the table.

[The information referred to follows, tab E may be found in subcommittee files:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 29 1998

The Honorable Dan Burton
Chairman, Committee on Government
Reform and Oversight
House of Representatives
Washington, D.C. 20515-6143

Dear Mr. Chairman:

This is in response to issues raised during the April 22, 1998 hearing, "Clinical Trial Subjects: Adequate FDA Protections?" Several questions were raised with respect to clinical trials conducted by the New York State Psychiatric Institute using fenfluramine. In addition, you asked for information regarding control groups in clinical trials. Questions and answers are set forth below.

1. **When was the first time the Food and Drug Administration knew of the experiment by the New York State Psychiatric Institute (NYSPI)?**

We are assuming that the NYSPI experiment to which you are referring was the one published in the September 1997 Archives of General Psychiatry, "Neuroendocrine Response to Fenfluramine Challenge in Boys: Associations with Aggressive Behavior and Adverse Rearing" (Archives study). The Food and Drug Administration (FDA or the Agency) became aware of the Archives study when it was discussed at a March 4, 1998 meeting of the National Bioethics Advisory Commission. FDA's reading of the paper indicated that the study would have qualified for exemption from requirements under the investigational new drug (IND) regulations at the time it was conducted.[1] Information

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[1]The use of fenfluramine in this study appears to have met the requirements for exemption from IND regulations contained in 21 CFR Section 312.2(b), promulgated in 1987. In 1997, because fenfluramine was no longer being marketed, FDA's Division of Neuropharmacologic Drug Products (the Division) notified investigators, who to its knowledge were conducting clinical studies using fenfluramine, that FDA no longer recognized the exemption and that such studies needed to be in compliance with IND requirements (Tab A). In response to this notice, the Division was informed of ongoing clinical studies using fenfluramine at NYSPI (Tab B). With respect to the use of fenfluramine in children, only one protocol provided for the inclusion of pediatric subjects (ages 12-26); the sponsor

provided to the National Institutes of Health, Division of Human Subject Protection, Office for Protection from Research Risks (OPRR), indicated that the use of fenfluramine in this Archives study was terminated in August 1995, more than 2 years prior to the voluntary withdrawal of fenfluramine from the market by the manufacturer, at FDA's request, because of its association with heart valve damage.

2. What is the policy of FDA in reviewing the consent papers on projects that come to FDA for approval?

For human drug studies performed under an IND, FDA's Center for Drug Evaluation and Research (CDER) generally does not receive the informed consent form. If a CDER review division receives the informed consent form with an IND application or in response to a request, the division obtains a review of the informed consent form by the CDER Division of Scientific Investigations in the Office of Compliance. For biologic studies performed under an IND, FDA's Center for Biologic Evaluation and Research routinely requests the informed consent form and reviews those forms which it receives. For medical device studies performed under an Investigational Device Exemption (IDE), FDA's Center for Devices and Radiological Health requires the submission of, and reviews, the informed consent form for all investigational studies. FDA also reviews informed consent forms during audits of specific studies after a marketing approval application is received.

3. How often does FDA review clinical trials to see that they are conforming to the consent? How often does FDA review to see what if any change has occurred in the protocol with regard to the pharmaceuticals that are being tested?

Review of a clinical trial to assess conformance to the consent occurs only when a study in support of a new drug application or a premarket approval application for a device is audited as part of a marketing approval review. Protocol changes which significantly affect the safety of subjects must be submitted before the changes are implemented, but the sponsor is not required to await FDA review before proceeding. Annual reports of ongoing INDs/IDEs must be submitted, including a summary of all serious adverse experiences and safety reports submitted during the year. Significant modifications in phase 1 IND protocols not previously reported must be described in the annual report.

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indicated that this protocol is not proceeding pending review of echocardiogram findings from adult protocols.

4. Has the FDA examined the IRB of the New York State Psychiatric Institute to see if there are conflicts of interest? What has FDA done in this case to look at the situation in terms of the makeup of that IRB?

The last inspection of the NYSPI Institutional Review Board (IRB) was in March 1993. No significant problems were found. No conflicts of interest were identified at that inspection. Review of membership is a standard part of an IRB inspection and the Establishment Inspection Report review (composition, conflict-of-interest). The IRB is due for reinspection in 1998.

5. Is there written Agency policy regarding informed consent for children? Where a parent consents for a child, are there rules or practice regarding obtaining a child's "assent"?

With regard to informed consent for children, FDA regulations pertaining to the protection of human subjects and informed consent apply. See, Title 21 Code of Federal Regulations (CFR) Part 50, Subparts A and B. The legally effective informed consent of the subject or the subject's legally authorized representative must be obtained before enrollment in a clinical trial. FDA's regulations define "legally authorized representative" as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subjects' participation in the research (see, 21 CFR Section 50.3(l)). Thus, parents, legal guardians, and/or others may have the authority to give permission to enroll children in research, depending on applicable State and local law of the jurisdiction in which the research is conducted.

IRBs review clinical investigations regulated by FDA. The primary purpose of such review is to assure the protection and rights of human subjects. Regulations pertaining to IRBs are at 21 CFR 56.[2] Many IRBs require investigators to obtain the permission of one or both of the parents or guardian (as appropriate) and the assent of children who possess the intellectual and emotional maturity to comprehend the concepts

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[2]With respect to IRB membership, FDA regulations provide that if "an IRB regularly reviews research that involves a vulnerable category of subjects, such as children . . . consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects" (see, 21 CFR Section 56.107(a)).

involved.[3] Some IRBs require two documents, a fully detailed explanation for parents and older children to read and sign, and a shorter simpler one for younger children.

In order for the IRB to approve research covered by FDA regulations, 21 CFR Section 56.111(a) states that it shall determine that certain requirements are satisfied including that: risks to subjects are minimized and are reasonable in relation to anticipated benefits; selection of subjects is equitable; informed consent is sought and appropriately documented; the research plan provides for monitoring data to ensure safety of subjects; and there are provisions to protect the privacy of subjects. Furthermore, 21 CFR Section 56.111(b) provides that additional safeguards must be included to protect subjects, such as children, who are likely to be vulnerable to coercion and undue influence.

6. **What are Agency regulations and/or policies with respect to payments to subjects participating in clinical trials? Are there specific regulations/policies pertaining to payments to parents of children participating in clinical trials?**

There are no specific Agency regulations with respect to payments to subjects participating in clinical trials or to payment to parents of children participating in clinical trials. The regulations, however, do require that an investigator seek consent under circumstances that minimize the possibility of coercion or undue influence (see, 21 CFR Section 50.20). FDA does have an "information sheet" that provides some guidance on payments (Tab D). FDA's Office of Health Affairs published a series of "information sheets" to help IRBs carry out their responsibilities for protection of research subjects (Tab E). The information sheet, "Payment to Research Subjects," notes that payment is not considered a benefit but rather a recruitment incentive. It states that the amount and schedule of payments should be presented to the IRB at the time of initial review. The IRB should review the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence.

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[3] See also, FDA's guideline, "Good Clinical Practice: Consolidated Guideline," which recommends obtaining the assent of children who are subjects in clinical trials (Section 4.8.12) (Tab C).

7. Was the consent form for the NYSPI study changed to reflect the new information on fenfluramine?

The Archives study at issue was completed prior to the withdrawal of fenfluramine from the market because of its association with heart valve damage.

8. Were the parents informed that there was heart damage or suspected heart damage in adults taking fenfluramine? Did they continue to keep their child in the study after they were informed of that?

The Archives study was completed prior to the withdrawal of fenfluramine from the market because of its association with heart valve damage.

9. Could you give us a breakdown on how you determine what control groups are appropriate for an IND?

Typically, the sponsors of the investigational product propose protocol designs based on what they believe will generate statistically relevant, clinically useful information, and are in keeping with generally accepted ethical principles. The Agency is available for early consultation about trial design and related issues if the sponsors request it (21 CFR Section 312.41). The Agency reviews the IND proposal and decides whether it is appropriate for the study to proceed, taking into account the safety of the human subjects and the scientific quality of the clinical investigation and likelihood that it will yield data of the quality necessary to support marketing approval. The sponsor must commit to proceed under the oversight of an appropriate IRB. The study can then proceed at a particular site only if the IRB approves it.

As you know, the approval of a new drug or a new indication must be based on adequate and well-controlled studies. Regulations at 21 CFR Section 314.126 describe the characteristics of adequate and well-controlled studies. The regulation notes that, in general, five kinds of control groups are recognized: placebo concurrent control, dose-comparison concurrent control, no treatment concurrent control (the control group gets no active drug but is not given a placebo either; the group is merely under observation), active treatment concurrent control, and historical control. Concurrent means that the treated and the control groups were studied at the same time and typically implies randomization to one of the two groups. "Placebo control" does not necessarily mean that the placebo group gets no therapy. More commonly, particularly in drug studies for serious illness needing treatment, placebo-controlled trials are really "add-on" trials

in which subjects are already receiving standard therapy and then are randomized to receive either the investigational therapy or placebo in addition to the continued standard therapy.

No general preference is expressed in the various regulations cited above for any one type of study design, but the study design chosen must be adequate to the task. Thus, in discussing historical controls, the regulation notes that, because it is relatively difficult to be sure that historical control groups are comparable to the treated subjects with respect to variables that could affect outcome, use of historical control studies usually are reserved for special circumstances, such as cases where the disease treated has high and predictable mortality (e.g., certain malignancies) and those in which the drug effect is self-evident (e.g., a general anesthetic).

Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are study designs in which a difference is intended to be shown between the test article and some control. The alternative study design generally proposed to these kinds of studies is an active treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent. There are circumstances in which this is a fully valid design. Active-controls are usually used in antibiotic trials, for example, because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. In many cases, however, the active-control design may be simply incapable of allowing any conclusion as to whether or not the test article is having an effect.

In many situations, deciding whether an active-control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment influenced by available evidence. If, for example, examination of prior studies of a proposed active-control reveals that the test article can very regularly be distinguished from placebo in a particular setting (subject population, dose, and other defined parameters), an active-control design may be reasonable if it reproduces the setting in which the active-control has been effective.

It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early escape mechanisms can be built into the study so that subjects

will not undergo prolonged placebo treatment if they are not doing well. In some cases, randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are assigned randomly to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint.

IRBs may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials in which the control group actually would receive no treatment obviously are not ethically acceptable where existing treatment is life-prolonging, regardless of any advantages in interpretation of results. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable. It is critical, however, to review the evidence that harm would result from denial of active treatment. Alternative study designs, especially active-control studies, may not be informative. A study design that will not be informative is, likewise, not acceptable because such a study results in exposing subjects to risk without being able to collect useful information to make that risk worthwhile.

* * *

For your information, in April 1998, FDA became aware that OPRR was investigating the Archives study.

In addition to the above-noted questions raised on April 22, following the hearing, your staff member, Ms. Laurie Taylor, asked whether FDA was looking into the issues raised in the testimony of Mr. and Mrs. Joe Foster. We asked CDER's Division of Scientific Investigations to review the testimony and it concluded that further investigation was warranted. We will report to you when its investigation is complete. Please note that the existence of this investigation is confidential and we ask, therefore, that the Committee not publish or otherwise make public this information.

Information contained in footnote 1, including the enclosures, contains confidential commercial information protected from disclosure to the public under the Freedom of Information Act (FOIA) (5 U.S.C. §552) and FDA's regulations implementing FOIA. We ask that the Committee not publish or otherwise make public this information. We would, of course, be glad to discuss with the Committee staff the confidentiality of any specific information.

Further information with respect to fenfluramine will be provided in our response to your May 19, 1998 request for information and document request. In the meantime, if you have further questions, please do not hesitate to contact us.

Sincerely,

Melinda K. Plaisier

per Diane E. Thompson
Associate Commissioner
for Legislative Affairs

5 Enclosures

cc: The Honorable Henry A. Waxman
Ranking Minority Member
Committee on Government Reform
and Oversight

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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NOV 20 1997

IND 25,419

J. John Mann, M.D.
The New York Hospital-Cornell Medical Center
The Payne Whitney Clinic
525 East 68th Street
New York, New York 10021

Dear Dr. Mann:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for fenfluramine hydrochloride.

We acknowledge receipt of your amendment dated September 18, 1997, providing for your annual report.

There has been evidence linking the combined use of fenfluramine and phentermine or dexfenfluramine and phentermine with valvular heart disease. As a result of this new information, the manufacturers of Pondimin (fenfluramine hydrochloride) and Redux (dexfenfluramine hydrochloride) have agreed to withdraw these products from the market and FDA has recommended that patients stop taking these drugs.

The Division is therefore requiring that all studies involving the use of fenfluramine or dexfenfluramine include pre-exposure and post-exposure echocardiograms, to investigate the possibility of drug-related valvular changes. Therefore, if you intend to continue using fenfluramine, we require that you submit an amendment to your IND providing for a change in your protocol to incorporate echocardiograms into the safety monitoring.

We additionally request that you clarify the following items in regard to your IND:

- Dosimetry information on the exposure to target organs from 18-FDG and 15-H_2O is lacking. Please provide this information.

- We note that your annual report includes the use of intravenous clomipramine, which is an investigational drug. Do you have a separate IND for intravenous clomipramine? If not, the Agency will require that the supporting chemistry and manufacturing information associated with this drug be submitted to your IND.

TAB A

We request that you formally respond to the above items within two months from the date of this letter.

If you have any questions concerning this IND, please contact Mr. Paul David, Project Manager, at (301) 594-5530.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

COLUMBIA UNIVERSITY
COLLEGE OF PHYSICIANS & SURGEONS
DEPARTMENT OF PSYCHIATRY

FedEx

Telephone: (212) 543-5571
FAX: (212) 543-5517

January 9, 1998

Paul Leber, M.D.
Director, Division of Neuropharmacological Drug Products
Office of Drug Evaluation I, Center for Drug Evaluation and Research
Department of Health & Human Services
Food and Drug Administration
Rockville, MD 20857

RE: IND #25,419

Dear Dr. Leber:

Thank you for your letter of November 20. I would like to respond as follows.

1. We will perform echocardiograms before and after the fenfluramine challenge tests that are given to our research subjects. We would propose that since those cases that have two fenfluramine challenges, one before and one after treatment, that we do the first echocardiogram before an individual has the first fenfluramine challenge and then the second echocardiogram 2-3 weeks after the second fenfluramine challenge. My own opinion is that these tests will show no enduring effects on heart valves. The reports of valvular changes in patients being prescribed fenfluramine on a long-term basis appear to involve structural changes in the valves, and these effects are unlikely to appear after a single challenge. Because potential effects are unlikely to appear until at least a couple of weeks have passed, we will do the echocardiograms, where possible, between 2-3 weeks after the second fenfluramine challenge.

2. I attach a list of protocols that are employing the fenfluramine challenge test at our instiution under the auspices of this IND, so that there is no ambiguity as to which studies are involved. All of these protocols follow the fenfluramine challenge protocol precisely as described in this IND file. We have previously provided you with this list, including other details of these protocols, with our previous communication.

3. Your letter was addressed to my old location at The New York Hospital, and I ask that you please note my new address at the New York State Psychiatric Institute. I had mentioned the change in location in my previous correspondence regarding this IND.

722 W. 168th Street New York, NY 10032

TAB B

4. You requested dosimetry information on exposure to target organs from ^{18}FDG and $^{15}H_2O$ water. Please note that we use 5 mCi of ^{18}FDG and $^{15}H_2O$ per scan. These doses are lower than those used for clinical imaging studies of metabolism or blood flow. Dosimetry information is as follows. Subjects get up to four ^{18}FDG brain studies using PET. The whole body dose is 0.041 rads/mCi and critical organ dose (bladder) is 0.629 rads/mCi.

If you require further information, please let me know.

Sincerely,

J. John Mann, M.D.
Professor of Psychiatry
Chief of Neuroscience

JJM:ag
attachments

cc: Dr. B. Timothy Walsh
Dr. Dr. John Rainer
Co-Chairs, NYSPI IRB

List of Protocols that are Employing the Fenfluramine Challenge Test at Our Institution, under the Auspices of this IND #28,419:

A sample of a revised IRB Protocol and consent form are attached for 1).
Final IRB-approved consent forms will be sent for all protocols when available.

1) IRB # 2692 (NYSPI); IRB #1221 (CPMC)
Neurobiological Studies of Antidepressants in Depression
PI: J. John Mann, M.D.

2) IRB # 2693 (NYSPI); IRB #1222 (CPMC)
Neurotransmitter Studies by PET Imaging
PI: J. John Mann, M.D.

3) IRB # 2824 (NYSPI); IRB # 1250 (CPMC)
Psychobiological Predictors of Suicidal Behavior in MDE
PI: J. John Mann, M.D.

4) IRB # 3195 (NYSPI); IRB # 1326 (CPMC)
FMR Imaging Study of the CNS Response to FEN Challenge
PIs: J. John Mann, M.D. and Daniel Pine, M.D.

5) IRB #3121 (NYSPI)
Biological Studies of Adolescents
PI: Laurence Greenhill, M.D.

NYSPI - New York State Psychiatric Institute
CPMC - Columbia Presbyterian Medical Center

federal register

Friday
May 9, 1997

Part II

Department of Health and Human Services

Food and Drug Administration

International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline; Notice of Availability

TAB C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96D-0219]

International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guideline entitled "Good Clinical Practice: Consolidated Guideline." The guideline was prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to define "Good Clinical Practice" and to provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. The guideline also describes the minimum information that should be included in an Investigator's Brochure (IB) and provides a suggested format. In addition, the guideline describes the essential documents that individually and collectively permit evaluation of the conduct of a clinical study and the quality of the data produced.

DATES: Effective May 9, 1997. Written comments may be submitted at any time.

ADDRESSES: Submit written requests for single copies of "Good Clinical Practice: Consolidated Guideline" to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573. Send two self-addressed adhesive labels to assist that office in processing your requests. Submit written comments on the guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Two copies of any comments are to be submitted, except that individuals may submit one copy. The "Good Clinical Practice: Consolidated Guideline" and received comments are available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Bette L. Barton, Center for Drug Evaluation and Research (HFD-344), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1032.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In the Federal Register of August 17, 1995 (60 FR 42948), FDA published a draft tripartite guideline entitled "Good Clinical Practice." In the Federal Register of August 9, 1994, FDA published draft tripartite guidelines entitled "Guideline for the Investigator's Brochure" (59 FR 40772) and "Guideline for Essential Documents for the Conduct of a Clinical Study" (59 FR 40774). The notices gave interested persons an opportunity to submit comments.

After consideration of the comments received and revisions to the guidelines, the three guidelines were consolidated into one guideline on good clinical practice. The consolidated guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held on April 30, 1996.

The guideline defines "Good Clinical Practice" and provides a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with Good Clinical Practice provides public assurance that the rights, well-being, and confidentiality of trial subjects are protected and that trial data are credible. The guideline should be followed when generating clinical data that are intended to be submitted to regulatory authorities. The principles established in this guideline should also be applied to other investigations that involve therapeutic intervention in, or observation of, human subjects.

The guideline also describes the minimum information that should be included in an IB; such as information on the drug's physical, chemical, and pharmaceutical properties, and its effect in humans; a suggested format for the IB is also provided. The guideline also describes the purpose of essential documents in a clinical study and explains whether the documents should be filed in the investigator's files or the sponsor's files.

This guideline represents the agency's current thinking on good clinical practices. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the Federal Register.

Interested persons may, at any time, submit to the Dockets Management Branch (address above) written comments on the guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this

document. A copy of the guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

An electronic version of this guideline is available via Internet. Type http://www.fda.gov/cder and go to the "Regulatory Guidance" section.

The text of the guideline follows:

Good Clinical Practice: Consolidated Guideline

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Introduction

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. *Glossary*

1.1 *Adverse Drug Reaction (ADR)*

In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 *Adverse Event (AE)*

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 *Amendment (to the protocol)*

See Protocol Amendment.

1.4 *Applicable Regulatory Requirement(s)*

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where a trial is conducted.

1.5 *Approval (in relation to Institutional Review Boards (IRB's))*

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

1.6 *Audit*

A systematic and independent examination of trial-related activities and documents to

determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOP's), good clinical practice (GCP), and the applicable regulatory requirement(s).

1.7 *Audit Certificate*

A declaration of confirmation by the auditor that an audit has taken place.

1.8 *Audit Report*

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 *Audit Trail*

Documentation that allows reconstruction of the course of events.

1.10 *Blinding/Masking*

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 *Case Report Form (CRF)*

A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

1.12 *Clinical Trial/Study*

Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 *Clinical Trial/Study Report*

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 *Comparator (Product)*

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 *Compliance (in relation to trials)*

Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

1.16 *Confidentiality*

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 *Contract*

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 *Coordinating Committee*

A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

1.19 *Coordinating Investigator*

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

1.20 *Contract Research Organization (CRO)*

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 *Direct Access*

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 *Documentation*

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 *Essential Documents*

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. "Essential Documents for the Conduct of a Clinical Trial").

1.24 *Good Clinical Practice (GCP)*

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 *Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)*

An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 *Impartial Witness*

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 *Independent Ethics Committee (IEC)*

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations, and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 *Informed Consent*

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

1.29 *Inspection*

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 *Institution (medical)*

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 *Institutional Review Board (IRB)*

An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 *Interim Clinical Trial/Study Report*

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 *Investigational Product*

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 *Investigator*

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 *Investigator/Institution*

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements."

1.36 *Investigator's Brochure*

A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the

investigational product(s) in human subjects (see 7. "Investigator's Brochure").

1.37 *Legally Acceptable Representative*

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 *Monitoring*

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOP's), GCP, and the applicable regulatory requirement(s).

1.39 *Monitoring Report*

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOP's.

1.40 *Multicenter Trial*

A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

1.41 *Nonclinical Study*

Biomedical studies not performed on human subjects.

1.42 *Opinion (in relation to Independent Ethics Committee)*

The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 *Original Medical Record*

See Source Documents.

1.44 *Protocol*

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline, the term protocol refers to protocol and protocol amendments.

1.45 *Protocol Amendment*

A written description of a change(s) to or formal clarification of a protocol.

1.46 *Quality Assurance (QA)*

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

1.47 *Quality Control (QC)*

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 *Randomization*

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 *Regulatory Authorities*

Bodies having the power to regulate. In the ICH GCP guideline, the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 *Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)*

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,

or

- Is a congenital anomaly/birth defect.

(See the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

1.51 *Source Data*

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 *Source Documents*

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

1.53 *Sponsor*

An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 *Sponsor-Investigator*

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 *Standard Operating Procedures (SOP's)*

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 *Subinvestigator*

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 *Subject/Trial Subject*

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 *Subject Identification Code*

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

1.59 *Trial Site*

The location(s) where trial-related activities are actually conducted.

1.60 *Unexpected Adverse Drug Reaction*

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

1.61 *Vulnerable Subjects*

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 *Well-being (of the trial subjects)*

The physical and mental integrity of the subjects participating in a clinical trial.

2. *The Principles of ICH GCP*

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. *Institutional Review Board/Independent Ethics Committee (IRB/IEC)*

3.1 *Responsibilities*

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfill its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

- Approval/favorable opinion;
- Modifications required prior to its approval/favorable opinion;
- Disapproval/negative opinion; and
- Termination/suspension of any prior approval/favorable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

3.1.6 When a nontherapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 *Composition, Functions, and Operations*

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 *Procedures*

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

(c) All adverse drug reactions (ADR's) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4 *Records*

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. *Investigator*

4.1 *Investigator's Qualifications and Agreements*

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom

the investigator has delegated significant trial-related duties.

4.2 *Adequate Resources*

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 *Medical Care of Trial Subjects*

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 *Communication with IRB/IEC*

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 *Compliance with Protocol*

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;

(b) To the sponsor for agreement; and, if required,

(c) To the regulatory authority(ies).

4.6 *Investigational Product(s)*

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 *Randomization Procedures and Unblinding*

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 *Informed Consent of Trial Subjects*

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the

satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 *Records and Reports*

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRF's and in all required reports.

4.9.2 Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRF's made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 *Progress Reports*

4.10.1 Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.6), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 *Safety Reporting*

4.11.1 All serious adverse events (SAE's) should be reported immediately to the sponsor except for those SAE's that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 *Premature Termination or Suspension of a Trial*

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 *Final Report(s) by Investigator/Institution*

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

5. *Sponsor*

5.1 *Quality Assurance and Quality Control*

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOP's to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 *Contract Research Organization (CRO)*

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

5.3 *Medical Expertise*

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 *Trial Design*

5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRF's and planning the analyses to analyzing and preparing interim and final clinical trial/study reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol, and conduct.

5.5 *Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee*

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

(b) Maintain SOP's for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (See 8. "Essential Documents for the Conduct of a Clinical Trial.")

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the appropriate regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed (see 4.9.3).

5.6 *Investigator Selection*

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;

(b) To comply with procedures for data recording/reporting; and

(c) To permit monitoring, auditing, and inspection (see 4.1.4).

(d) To retain the essential documents that should be in the investigator/institution files (see 8.) until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4, 4.9.5, and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 *Allocation of Duties and Functions*

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 *Compensation to Subjects and Investigators*

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 *Financing*

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 *Notification/Submission to Regulatory Authority(ies)*

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)), should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 *Confirmation of Review by IRB/IEC*

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

5.12 *Information on Investigational Product(s)*

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the investigator's Brochure as significant new information becomes available. (See 7. "Investigator's Brochure.")

5.13 *Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)*

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 *Supplying and Handling Investigational Product(s)*

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (See 8. "Essential Documents for the Conduct of a Clinical Trial.")

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 *Record Access*

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 *Safety Information*

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

5.17 *Adverse Drug Reaction Reporting*

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADR's) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 *Monitoring*

5.18.1 *Purpose.* The purpose of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

5.18.2 *Selection and Qualifications of Monitors.*

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOP's, GCP, and the applicable regulatory requirement(s).

5.18.3 *Extent and Nature of Monitoring.*

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 *Monitor's Responsibilities.*

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.8) and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorized procedures.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s) if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRF's and are consistent with the source data/documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRF's.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRF's.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRF's.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AE's) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, the applicable regulatory requirement(s), and indicated in the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

(p) Determining whether the investigator is maintaining the essential documents. (See 8. "Essential Documents for the Conduct of a Clinical Trial.")

(q) Communicating deviations from the protocol, SOP's, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 *Monitoring Procedures.*

The monitor(s) should follow the sponsor's established written SOP's as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 *Monitoring Report.*

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative.

5.19 *Audit*

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 *Purpose.*

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOP's, GCP, and the applicable regulatory requirements.

5.19.2 *Selection and Qualification of Auditors.*

(a) The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 *Auditing Procedures.*

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings or investigations.

(e) Where required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 *Noncompliance*

5.20.1 Noncompliance with the protocol, SOP's, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 *Premature Termination or Suspension of a Trial*

If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 *Clinical Trial/Study Reports*

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial/study reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 *Multicenter Trials*

For multicenter trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

5.23.2 The CRF's are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRF's should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of the coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRF's.

5.23.5 Communication between investigators is facilitated.

6. *Clinical Trial Protocol and Protocol Amendment(s)*

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 *General Information*

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 *Background Information*

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 *Trial Objectives and Purpose*

A detailed description of the objectives and the purpose of the trial.

6.4 *Trial Design*

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including (for example):

(a) Randomization.

(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRF's (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 *Selection and Withdrawal of Subjects*

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 *Treatment of Subjects*

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 *Assessment of Efficacy*

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.

6.8 *Assessment of Safety*

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 *Statistics*

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).

6.10 *Direct Access to Source Data/Documents*

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

6.11 *Quality Control and Quality Assurance*

6.12 *Ethics*

Description of ethical considerations relating to the trial.

6.13 *Data Handling and Recordkeeping*

6.14 *Financing and Insurance*

Financing and insurance if not addressed in a separate agreement.

6.15 *Publication Policy*

Publication policy, if not addressed in a separate agreement.

6.16 *Supplements*

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. *Investigator's Brochure*

7.1 *Introduction*

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRB's)/Independent Ethics Committees (IEC's) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRB's/IEC's. In the case of an investigator-sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 *General Considerations*

The IB should include:

7.2.1 *Title Page.* This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 *Confidentiality Statement.* The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 *Contents of the Investigator's Brochure.* The IB should contain the following sections, each with literature references where appropriate:

7.3.1 *Table of Contents.* An example of the Table of Contents is given in Appendix 2.

7.3.2 *Summary.* A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic.

and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 *Introduction.* A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 *Physical, Chemical, and Pharmaceutical Properties and Formulation.* A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 *Nonclinical Studies.*

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

Species tested;

Number and sex of animals in each group;

Unit dose (e.g., milligram/kilogram (mg/kg));

Dose interval;

Route of administration;

Duration of dosing;

Information on systemic distribution;

Duration of post-exposure follow-up;

Results, including the following aspects:

- Nature and frequency of pharmacological or toxic effects;
- Severity or intensity of pharmacological or toxic effects;
- Time to onset of effects;
- Reversibility of effects;
- Duration of effects;
- Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

Single dose;

Repeated dose;

Carcinogenicity;

Special studies (e.g., irritancy and sensitization);

Reproductive toxicity;

Genotoxicity (mutagenicity).

7.3.6 *Effects in Humans.*

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function).

Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s)).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experience with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 *Summary of Data and Guidance for the Investigator.*

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on

the pharmacology of the investigational product.

7.4 Appendix 1:

TITLE PAGE OF INVESTIGATOR'S BROCHURE (Example)

Sponsor's Name:

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 Appendix 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE (Example)

- Confidentiality Statement (optional)
- Signature Page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
5.1 Nonclinical Pharmacology
5.2 Pharmacokinetics and Product Metabolism in Animals
5.3 Toxicology
6. Effects in Humans
6.1 Pharmacokinetics and Product Metabolism in Humans
6.2 Safety and Efficacy
6.3 Marketing Experience
7. Summary of Data and Guidance for the Investigator

NB: References on

1. Publications
2. Reports

These references should be found at the end of each chapter.

Appendices (if any)

8. Essential Documents for the Conduct of a Clinical Trial

8.1 Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: (1) Before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.2.1	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	Information given to trial subject	To document the informed consent	X	X
	- Informed consent form (including all applicable translations)			
	- Any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	Signed agreement between involved parties, e.g.:	To document agreements		
	- Investigator/institution and sponsor		X	X
	- Investigator/institution and CRO		X	X (Where required)
	- Sponsor and CRO			X
	- Investigator/institution and authority(ies) (Where required)		X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.2.7	Dated, documented approval/favorable opinion of IRB/IEC of the following: - Protocol and any amendments - CRF (if applicable) - Informed consent form(s) - Any other written information to be provided to the subject(s) - Advertisement for subject recruitment (if used) - Subject compensation (if any) - Any other documents given approval/favorable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s).	X	X
8.2.8	Institutional review board/independent ethics committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	Regulatory authority(ies) authorization/approval/notification of protocol (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
8.2.12	Medical/laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects	X	X
8.2.14	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
8.2.15	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
8.2.16	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial.		X
8.2.17	Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	Master randomization list	To document method for randomization of trial population		X (third party if applicable)
8.2.19	Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 *During the Clinical Conduct of the Trial*

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.3.1	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	Any revisions to: - Protocol/amendment(s) and CRF - Informed consent form - Any other written information provided to subjects - Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents that take effect during trial	X	X
8.3.3	Dated, documented approval/favorable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the following: - Protocol amendment(s) - Revision(s) of: - Informed consent form - Any other written information to be provided to the subject - Advertisement for subject recruitment (if used) - Any other documents given approval/favorable opinion - Continuing review of trial (see 3.1.4)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X
8.3.4	Regulatory authority(ies) authorizations/approvals/notifications where required for: - Protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	Curriculum vitae for new investigator(s) and/or subinvestigators	(See 8.2.10)	X	X
8.3.6	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	Updates of medical/laboratory/technical procedures/tests - Certification or - Accreditation or - Established quality control and/or external quality assessment or - Other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	Documentation of investigational product(s) and trial-related materials shipment	(See 8.2.15)	X	X
8.3.9	Certificate(s) of analysis for new batches of investigational products	(See 8.2.16)		X
8.3.10	Monitoring visit reports	To document site visits by, and findings of, the monitor		X
8.3.11	Relevant communications other than site visits - Letters - Meeting notes - Notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	Signed, dated, and completed case report forms (CRF's)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.3.15	Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 4.11.2 and 5.16.2	X (where required)	X
8.3.18	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
8.3.21	Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	Subject enrollment log	To document chronological enrollment of subjects by trial number	X	
8.3.23	Investigational product(s) accountability at the site	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRF's	X	X
8.3.25	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 *After Completion or Termination of the Trial* After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.4.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
8.4.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	Audit certificate (if required)	To document that audit was performed (if required) (see 5.19.3(e))		X
8.4.5	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X

	Title of Document	Purpose	Located in Files of	
			Investigator/Institution	Sponsor
8.4.5	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	Final report by investigator/institution to IRB/IEC where required, and where applicable, to the regulatory authority(ies) (see 4.13)	To document completion of the trial	X	
8.4.8	Clinical study report (see 5.22)	To document results and interpretation of trial	X (if applicable)	X

Dated: April 30, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97-12138 Filed 5-8-97; 8:45 am]

BILLING CODE 4160-01-F

PAYMENT TO RESEARCH SUBJECTS

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when benefit to subjects is remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Recruiting Study Subjects."

TAB D

Mr. BURTON. Mr. Foster, you can remain seated and, Mrs. Foster and Dr. Vukov, would you please stand and raise your right hands?

[Witnesses sworn.]

Mr. BURTON. Mr. Foster, why don't you pull the microphone close to you. Oh, Mrs. Foster, you're going to speak for your husband?

Mrs. FOSTER. Yes.

Mr. BURTON. OK. Would you pull the microphone close to you, please, then. And a little bit closer, if you would. And if you'd proceed with your opening statement.

STATEMENTS OF BARBARA FOSTER, ACCOMPANIED BY JOE FOSTER, CLINICAL TRIAL PARTICIPANT; AND JUDITH VUKOV, M.D., PSYCHIATRIST

Mrs. BARBARA FOSTER. All right. Thank you very much for allowing me to be here today. I'm grateful for the opportunity. I wish my husband could speak for himself, but I'm going to read this statement about what happened to him.

Prior to 1996, my husband had spent most of his adult life building a career in the real estate business. During most of the 1970's and 1980's, he was president and part-owner of Century 21 of North Texas, Oklahoma, and Arkansas. After selling that company, he spent most of his time upgrading and developing his real estate properties in Texas and southern California.

During the 1990's, the market suffered substantially, but he fought the good fight and by 1996 real estate generally, and my husband's real estate interests in particular, had turned the corner and the future was bright.

We had a nice home in Lake Forest with our son Joseph, who attended the local high school.

In October 1996, Joe made a decision that changed the rest of his life and my life. Joe read an advertisement soliciting individuals with high blood pressure to assist in the evaluation of a new drug to help people like him. He was interested enough to telephone the Anaheim Heart Research Institute, which was conducting a test of a new drug to control blood pressure made by Bristol Myers Squibb Co.

After telephoning the Institute on October 18, 1996, Joe was invited to come to the Institute for further discussions. Dr. Melvin Tonkon was the chief clinical investigator for this test. Both Joe and I went to Dr. Tonkon's office on October 22, 1996, and Joe had a brief physical examination administered by Dr. Tonkon's staff. Joe was then told that he qualified for the research on the basis of that medical examination. He was instructed to stop taking Lotensin, the medication that he had been taking to control his high blood pressure, and to begin taking the pills which Dr. Tonkon's office gave him. During that interview, Joe was assured that the research had been approved by, and was controlled by, the Food and Drug Administration, and that if anything happened to him as a result of his participation in this study, his health care needs would be looked after and paid for by the company which made the drug.

Six days after becoming a participant in this study, Joe suffered a major heart attack, followed by a debilitating stroke. Immediately prior to the heart attack, when he was feeling weak and sweaty

and had a pain in his arm, I called Dr. Tonkon and he said that I should either take Joe to his office or go to the emergency room. I took Joe to the emergency room since Dr. Tonkon's office was about an hour's drive from my home. Joe remained in the hospital for 26 days and I really doubted that he would come out alive. Following that, he was transferred to a nursing home where he spent 28 days and then was put back into the hospital for 31 days. Joe was then forced to go home since we could no longer pay for the hospital costs and had no insurance.

After Joe's heart attack, I spoke to Dr. Tonkon. Dr. Tonkon told me that he and the drug company had no responsibility because Joe had been given a placebo. In other words, Joe received no medication at all, and therefore, the doctor said he had no responsibility, even though he had taken Joe off of his medication which had been prescribed by Dr. Luppi, Joe's prior physician of many years. In fact, Dr. Tonkon had represented that he would confer with Dr. Luppi to make sure that Joe's participation in the study was safe, but I subsequently found that he never did so.

In a later conversation, Dr. Tonkon told me he had just reviewed Joe's records and that Joe should never have been accepted into the study in the first place. On two occasions, I was also told by Dr. Tonkon's office to immediately send back the pills they had given Joe. Had Joe known that Dr. Tonkon was given him nothing to replace his medication, which had kept his high blood pressure under control in the past, Joe would never have agreed to the test, nor would I have let him do so.

During Joe's interviews with Dr. Tonkon's representatives, he and I were told that the U.S. Food and Drug Administration had approved the test methods as well as the drug he would be given during the test and we relied upon the reputation and integrity of the Food and Drug Administration in agreeing to assist in the test. Joe and I were lead to believe that in so doing, he would be looked after by the Food and Drug Administration, the drug company that made the product, and by Dr. Tonkon himself.

Instead of looking after him, all three of those entities have run from Joe. After permitting Bristol Myers to use its name to induce Joe and many others to participate in this study, the Food and Drug Administration has done nothing to remedy this situation or help Joe. In fact, they have refused to produce documents of any type relating to this FDA-approved study, notwithstanding Joe's Freedom of Information Act request for that information.

After permitting Bristol Myers and Dr. Tonkon to hold themselves out as FDA-approved physicians and health care providers, the FDA has done nothing to cause them to provide health care assistance to Joe or to protect others from suffering the damage that their actions have caused Joe.

After telling Joe that he would speak with his physician who had prescribed the medication Joe was on before taking him off his medication, we now find that Dr. Tonkon never did so.

After giving Joe a medical examination, Dr. Tonkon did not wait for test results which should have disqualified him from participating in the tests. And after Dr. Tonkon received those results, he did nothing to inform us of the health risks involved.

After initially advising our lawyers that Bristol Myers had agreed to pay all of Joe's medical bills, Dr. Tonkon now says he never told them that.

After telling Dr. Tonkon that they would reimburse Joe for his medical expenses, Bristol Myers has refused to do so.

Since joining in the Bristol Myers research and suffering the resulting heart attack and stroke, Joe's life is forever changed. Our business is bankrupt because he can no longer run it. Our son Joe cannot continue his education because we cannot afford it. There are over $240,000 in unpaid medical bills. Joe cannot get the medical care he needs because we cannot afford it. He can no longer drive a car, nor walk across a room alone. When he does use a walker, he can only go 30 or 40 feet before he must sit and rest. He is often reduced to needing bottled oxygen so that he can breathe properly. Joe will never be able to play with our son Joe, earn a living, mow the yard, or even take an evening walk with me, as we used to do. All of the things in which he took so much pleasure in the past are gone forever.

[The information referred to follows:]

HIGH BLOOD PRESSURE?

Volunteers Needed for Clinical Research Studies

Anaheim Heart and Research Institute is conducting clinical studies for high blood pressure. These studies are funded by pharmaceutical companies at no cost to volunteer participants.

Participants receive the following care:

- Free office visits with a board certified cardiologist
- Free study medication
- Free lab tests and EKG's
- Some studies have patient reimbursement

CALL (714) 635-9146

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1211 W. La Palma #207, Anaheim, CA 92801

Mrs. BARBARA FOSTER. And Joe has just a little bit he'd like to say, please.

Mr. JOE FOSTER. I simply would like to let you know that, you know, the FDA, under their regulations with Dr. Tonkon and Bristol Myers, that they would no longer allow someone to be treated like me, giving them nothing. And because of this, you know, they can't do anything for me, but they could stop this in the past with anybody else in the condition that I'm being put in.

Mr. BURTON. Thank you, Mr. Foster, Mrs. Foster. Dr. Vukov, would you like to make an opening statement?

Dr. VUKOV. Yes, Mr. Chairman and members of the committee, I thank you for the opportunity to tell you of a tragedy in my life that I learned is all too common in the field of scientific research.

My name is Dr. Judith Vukov, and I am not only a grieving mother, but also a practicing psychiatrist and a provider of FDA-approved psychiatric drugs. My 25-year-old daughter, my only child, died 4½ years ago, which was 54 days after entering the clinical trials for Resperidone versus Haldol. The trials were sponsored by Jansenn Pharmaceuticals and conducted by a team of doctors from UCLA at one of the State hospitals in California. The clinical trials were headed by a supposed renowned researcher, Dr. Robert P. Liberman, who was also the head of schizophrenic research at the Veterans Administration in Los Angeles and at the Neuropsychiatric Institute at UCLA.

The unofficial death certificate states that my daughter died of aspirin toxicity and undue delay in diagnosis and suicide. In my opinion and that of many others, this was a quick and superficial explanation of why and how my daughter died. The emergency room notes, the urgent care notes, and the sparse notes from Unit 45, the research unit, serve to document that Abby was not only the victim of egregious medical malpractice at the emergency room and the urgent care, but also the unwitting victim of fraud, misrepresentation, and neglect by the research staff of Unit 45.

Abby died because she was placed at risk as a research subject. And even when her condition became life-threatening, she was neglected and abandoned. The research records revealed there was no attempt to intervene either medically or psychiatrically. The research staff, in an attempt to cover up their responsibility for her death, have stated on numerous occasions that Abby took 300 aspirin while she was in my care in approximately an hour and a half, and even attempted to deny that she was a subject of research and to this day they still deny it.

Last year, I requested a full Federal review of Abby's research experience, and I have requested that the FDA place a moratorium on all research involving human psychiatric subjects at UCLA, the Veteran's Administration, and Jansenn—and those sponsored by Jansenn Pharmaceuticals until a thorough Federal investigation could take place. I have heard nothing from the FDA. I did receive one phone call saying that they would get back to me.

There was an investigation by the California Department of Health Services. Among some of the complaints that they cited, there were no doctors or nurses caring for my daughter during the last 18 days of her life. The only people there apparently were aides, garbage men, and a social worker.

No. 2, the research team misrepresented Unit 45 as an acute care unit when in fact it was licensed as an intermediate care facility, which is also known as a group home, which has a much lower standard of care. But even at this lower standard of care, these people broke the State health code.

No. 3, they noted that she had been administered Tylenol 13 times by the non-professional staff during the last week of her life and there were no physician notes explaining why or for what reason. There was also no treatment plan done during any of the 54 days.

A further indication of the quality of care on Unit 45, on the night that Abby lay dying 15 miles from the research unit, the research staff recorded her as alive and well and in bed. Additionally, it appears from information received in a Freedom of Information request that the research team adjusted her—changed her diagnosis to fit the protocol requirements and ignored her long medical history, which I had provided to them.

The FOI request revealed that, No. 1, to be included in the research, one must have a clear-cut diagnosis of schizophrenia. The UCLA team ignored their own findings and those of many previous doctors which were consistent with a mood disorder and the diagnosis of many previous psychiatrists and labeled her schizophrenic. So—I believe so they could use her in the program.

No. 2, the subject should not have been diagnosed with a neurologic condition. Abby had Tourette's Syndrome, Sydenham's Chorea as a child; and, 1 month prior to admission to Unit 45, she had been assaulted and had suffered a head injury on two occasions.

When Abby's condition deteriorated and dramatically changed for the worse, as documented by the sparse records I was able to uncover, instead of reverting to standard practice, the researchers utilized behavior modification and "shunning," a practice which had been outlawed by Los Angeles Patient's Rights years before.

After her death, the UCLA research team disavowed Abby as a research subject. However, under the Code of Federal Regulations, altering her medication for the purposes of research automatically placed her in the research.

For Abby, the quality of care was more than deficient. My daughter was abandoned through neglect and traumatized by their particular brand of research. The attitude of the UCLA team to my daughter's death and the findings of the investigations can be summed up in a statement by the head of the team during a fact-finding event. When asked if he kept reports about Abby's death, he said, "If I saved all the material that came across my desk, there wouldn't be any room for me to sit down." Thus, the findings about my daughter's tragic death only filled his wastebasket.

Speaking now as a psychiatrist, I once believed that research subjects received the best care because the information passed on as facts to us in the field is what we base our informed decisions on. I now use every new drug with trepidation, knowing that what was uncovered in the investigation of Abby's death and that of others is systemic and pervades all levels of the research community.

Let me add, I've spent about 4,000 hours investigating this—myself and with some other people, because it was very, very difficult

to even get to square one. Abby's case was pivotal in the L.A. County Department of Mental Health decision to bar all conservatees from participation in research of any kind in that county or L.A. County conservatees. To sum up my feelings and those of others, the L.A. Patient's Rights Group said to me that if this had happened in a private hospital under their jurisdiction, they would have shut it down.

Mr. Chairman, I am convinced that my daughter was only one of potentially thousands of mentally ill patients who have had adverse reactions and/or death due to clinical research and then were simply abandoned and never reported to the FDA or to the National Institute of Mental Health. Let me also add that scientific research must continue, of course. I rely on it for my patients. But it is imperative that the protection of the human subject comes first, over and above the outcome of the research.

No. 2, and I also believe that, once it becomes known that there has been fraud or scientific misconduct, that group should no longer be receiving funds from NIMH or FDA.

Thank you.

[The prepared statement of Dr. Vukov follows:]

Mr. Chairman and Members of the Committee, I thank you for the opportunity to tell you of a tragic occurrence in my life that, I have learned, is all too common, in the field of scientific research.

My name is Judith Vukov, and I am not only a grieving mother but also a practicing psychiatrist and a provider of FDA approved psychiatric drugs. My twenty-five year-old daughter, Abby, died four and a half years ago. Fifty four days after entering the clinical trials for Resperidone versus Haldol, sponsored by Jansenn Pharmaceuticals and conducted by a UCLA team of researchers at the world renowned Camarillo State Hospital ResearchUnit 45, a satellite of UCLA/NPI. The clinical trials were headed by Dr. Robert P. Liberman who was also the head of schizophrenic research at the Los Angeles Veterans Administration and Neuropsychiatric Institute/ UCLA.

The official death certificate states that she died of aspirin toxicity and UNDUE DELAY IN DIAGNOSIS. In my opinion and that of many others this was a quick superficial explanation of why and how my daughter died. The emergency room notes, the urgent care notes and the sparse notes from Unit 45 serve to document that Abby was not only the victim of egregious medical malpractice at the emergency room and the urgent care but also the unwitting victim of fraud, misrepresentation and neglect by the research staff of Unit 45.

Abby died because she was placed at risk as a research subject and even when her condition became life-threatening she was neglected. The research records revealed that there was no attempt to intervene either medically or psychiatrically. The research staff, in an attempt to cover up their responsibility for her death have stated on numerous ocassions that Abby took 300 aspirin while she was in my care, and even attempted to deny that she was the subject of research.

Last year I requested a full federal review of Abby's research experience and I have requested that the FDA place a moratorium on all research involving human psychiatric subjects at UCLA, the Veteran's Administration and Jansenn Pharmaceuticals until a thorough federal investigation can take place. I have heard nothing from the Food and Drug Administration.

An investigation by The California Health Department revealed in part that:

(1) that there were no nurses or doctors caring for my daughter during the last 18 days of her life;

(2) that the research team misrepresented Unit 45 as an "acute care unit" when in fact it was an "intermediate care facility" also known as a group home;

(3) that she had been administered Tylenol thirteen times by the non-professional staff during the last week and that there were no physician notes explaining why;

(4) that no treatment plan had been compiled during any of the 54 days she was residing on Unit 45.

On the night Abby lay dying 15 miles from the research unit the night staff recorded her as alive and well and in bed. Additionally, it appears from information received in a Freedom of Information request that the research team adjusted her diagnosis to fit the protocol requirements and ignored her extensive and serious medical history.

The Freedom of Information request revealed that:

(1) to be included in the research one must have a clear-cut diagnosis of schizophrenia. The UCLA team ignored their own findings which were consistent with a mood disorder and the diagnosis of many previous psychiatrists, and labeled her schizophrenic so that they could use her as a subject;

(2) the subject should not have been diagnosed with a neurologic condition. Abby had Tourette's Syndrome, Sydenham's Chorea and in the month prior to admission to Unit 45 she had been assaulted and had suffered a head injury on two occasions.

When Abby's condition deteriorated and dramatically changed for the worse as documented by the sparse records I was able to uncover, instead of reverting to standard practice the researchers utilized behavior modification and "shunning" a practice which had been outlawed by Los Angeles Patient's Rights years before.

After her death, the UCLA research team disavowed Abby as a research subject. However, under the Code of Federal Regulations altering her medication for the purposes of research automatically placed her in the research.

For Abby, the quality of care was more than deficient. My daughter was abandoned through neglect and traumatized by their particular brand of research.

The attitude of the UCLA team to my daughter's death and the findings of the investigations can be summed up in a statement by the head of the team during a fact finding event. When asked if he kept reports about Abby's death he said "if I saved all of the material that came across my desk there wouldn't be any room for me to sit down." Thus the findings about my daughter's tragic death only filled his wastebasket.

Speaking now as a psychiatrist I once believed that research subjects received the best care because the information passed on as facts to us in the field is what we base our informed decisions on. Based on what I have learned since Abby's death, I use every new drug with trepidation knowing that what was uncovered in the investigation of Abby's death and that of others is systemic and pervades all levels of the research community.

Abby's case was pivotal in the Los Angeles County decision to bar all conservatees from participation in research of any kind. To sum up my feelings and those of others, the LA Patient's Rights group said to me that if this had happened in a private hospital under their jurisdiction they would have shut it down.

Mr. Chairman, I am convinced that my daughter was only one of potentially thousands of mentally ill patients who have had adverse reactions to clinical research and then were simply abandoned and never reported to the FDA or to the National Institutes of Mental Health. There must be better monitoring systems in place to protect these people who are unable to protect themselves in the face of those who wish to promote the interests of science.

Mr. BURTON. Thank you, Dr. Vukov.

Let me just ask a few questions.

First of all, Mr. Foster—if you can answer for your husband, Mrs. Foster—would you pull the microphone closer, please? What was your husband's blood pressure problem before he went into this test?

Mrs. FOSTER. He'd had high blood pressure.

Mr. BURTON. How high was it?

Mrs. FOSTER. It was—sometimes it was 180/110.

Mr. BURTON. So, without his medication, his doctor thought he would be in real jeopardy?

Mrs. FOSTER. Yes, that's correct.

Mr. BURTON. And when he went to this clinical study did he inform—I mean, they were aware that he had the high blood pressure problem, that's why they allowed him in?

Mrs. FOSTER. Yes. He was on a medication that was not controlling his blood pressure very well. In fact, he tried several different medications in the past 2 or 3 years, and so he was hopeful that this new drug that he was going to be trying would help control his blood pressure better than what he was taking.

Mr. BURTON. Were you led to believe that the pills that were given to him were blood pressure medication?

Mrs. FOSTER. Oh, yes.

Mr. BURTON. You didn't have any idea that they were a placebo?

Mr. BURTON. Had no idea whatsoever.

Mr. BURTON. Until he had the stroke and the heart attack?

Mrs. FOSTER. That's correct.

Mr. BURTON. I see. Dr. Vukov, you signed a consent form, I guess, for your daughter to be admitted?

Dr. VUKOV. Yes.

Mr. BURTON. I see. Now——

Dr. VUKOV. My daughter also signed it, violating the terms of her conservatorship.

Mr. BURTON. I see. You were aware of the kind of medication that they we're giving her?

Dr. VUKOV. That I thought they were giving her.

Mr. BURTON. So you had no idea what they were giving her?

Dr. VUKOV. Well, in the chart it said—there's a statement about placebo washout. Now I'm wondering if she was actually on medication.

Mr. BURTON. So you don't know? You have no way of knowing whether she was given a placebo or actually medication to help her with her problem?

Dr. VUKOV. When we tried to get the research records, we only got six pages, most of which were empty. And I know for a fact that there are many more pages because I sat with one of the research assistants and gave her a huge history on my daughter. And I called the APA even, and they said, "Oh, the researchers never give up their records." So I don't know.

Mr. BURTON. But you have asked the FDA and the relevant agencies for any bit of information that you could get on your daughter?

Dr. VUKOV. I didn't ask them to get me information on her. I wrote them a long letter last fall requesting an investigation—I

mean, you know, like a 10- or 12-page letter—and then I heard from the doctor that I wrote it to by phone and then he never got back to me. He said, "Why didn't you call me sooner?" Well, nobody knows who called him sooner because there's no information. I was—I'm a psychiatrist and I was stumbling around for a year and a half until I met the group that Adil Shamoo is involved with.

Mr. BURTON. I see.

Dr. VUKOV. And then, finally, things began to click and it all—you know, it started falling into place. Because I kept asking for records from the hospital, and even the hospital records were insufficient, and I didn't realize it was because I was looking for my kind of records when they didn't produce many records.

Mr. BURTON. I see.

Mr. Foster, you signed an informed consent form, right?

Mr. FOSTER. No.

Mr. BURTON. When you went into the program?

Mr. FOSTER. No.

Mr. BURTON. You did not sign an informed consent form?

Mr. FOSTER. No, I didn't.

Mr. BURTON. They put you into the program without you signing any form?

Mr. FOSTER. That's right.

Mr. BURTON. And they didn't tell you that you might be taking something other than a medication that would help your blood pressure?

Mr. FOSTER. No, they didn't.

Mr. BURTON. Did the doctor that you were talking to explain to you that there are risks you might be facing during these trials, these clinical trials?

Mr. FOSTER. No, he didn't.

Mr. BURTON. Did he tell you that there's a possibility that if you were taking something other than the medication that you were on that you might have a heart attack or a stroke?

Mr. FOSTER. No.

Mr. BURTON. He didn't tell you any of that?

Mr. FOSTER. No.

Mr. BURTON. What did he tell you?

Mr. FOSTER. He didn't tell me anything.

Mr. BURTON. Well, he must have told you something, I mean, when you're——

Mr. FOSTER. He spent two to 3 minutes with me at the most, and he was obviously in a hurry and he just buzzed through and said to his assistant, "Take care of him."

Mr. BURTON. OK. And what did the assistant do then?

Mr. FOSTER. The assistant gave me the pills and I went away and I took them, and they said, "Fill out the forms and we'll go over them when you come back."

Mr. BURTON. They said, "Take the pills"——

Mr. FOSTER. And I never came back.

Mr. BURTON. They said, "Take the pills and go off of your other medication."

Mr. FOSTER. Yes.

Mr. BURTON. And he didn't go into any details about the possible problems that you might encounter during this——

Mr. FOSTER. No.

Mr. BURTON. I'm sure, if you knew you might have been at risk, you wouldn't have taken those pills.

Mr. FOSTER. That's right; I wouldn't have.

Mr. BURTON. You would have stayed with your current medication. And you said right now that your medical bills are how much; $240,000?

Mr. FOSTER. That's the accumulation of, you know——

Mr. BURTON. And you don't have the ability to pay those?

Mr. FOSTER [continuing]. Months in the hospital and the clinic——

Mr. BURTON. OK. Well, we'll ask the FDA after a bit, how they deal with these sorts of problems. I think that's all I have.

Mr. Cummings.

Mr. CUMMINGS. Thank you very much. First of all, I want to say to all of you how sorry I am. I think the loss of a child is one of the most horrendous things one can ever experience and I'll tell you, I just listened to your stories, but I've heard similar stories in my district.

To Mr. and Mrs. Foster, I feel a special kinship to you because I've suffered from high blood pressure for 25 years. My blood pressure, at one point, was 180/130. I'm lucky to be here. And so, I owe you a special—by the way, it's normal now. It's like 120/88, thanks to medicine. But I want to—I owe a special debt to you for trying to do something to make a difference, and I'm so sorry that you had to suffer because of this. But I want you to understand that I appreciate what you tried to do.

Doctor, can you help me? I need some help from you, because you seem to know a lot about this. Tell me, why do they use placebos?

Dr. VUKOV. I think it's so there will be one clear-cut case of no medicine, no drugs. But placebos all have effects—everybody knows that in psychiatry—versus the medication that they're giving.

Mr. CUMMINGS. So is it supposed to be like——

Dr. VUKOV. A virgin territory.

Mr. CUMMINGS. So is it supposed to be like a psychological thing where you think you're taking something to make you better and——

Dr. VUKOV. Well, I think they have to eliminate that part from the research data.

Mr. CUMMINGS. So——

Dr. VUKOV. I call it "the psychological issues."

Mr. CUMMINGS. And in my dealings with—I practiced some medical malpractice law, and by the way, you all are evidence as to why we need to keep medical malpractice intact, but in my experiences there was always some kind of Institutional Review Board that looked at these kinds of things, and I'm just trying to figure out where those Institutional Review Boards come in with regard to approving trials and things of that nature. How does that——

Dr. VUKOV. Well, there is an Institutional Review Board called 'Friends West," but I saw no evidence that it did anything. I mean, the condition of care on that unit was so horrendous, after I found out what had happened, that I don't think they were there.

Mr. CUMMINGS. And in the hospitals where I have represented doctors it seemed as if there was a genuine concern that the local

folk wanted to have a certain level of control, as opposed to the FDA, and I guess that's what I'm becoming a little bit confused at, too, as to where does the FDA, where do you see the FDA responsibility in this whole episode, say with regard to your daughter? How does it play? I am just curious.

Dr. VUKOV. Where is the funding coming from?

Mr. CUMMINGS. Funding.

Dr. VUKOV. This group is still, according to the Internet, the NIMH Internet website, they're still receiving million-plus grants every year, unchecked. And I think that the FDA has got to get in there and stop the funding as soon as there's any indication of fraud. I mean, L.A. County stopped sending their conserved patients to research. That should have sent up a flag, for heaven's sakes. Even Channel 7 was there, or Channel 5 or something. And it was reported in the psychiatric newspapers and it was reported in the L.A. Times.

Mr. CUMMINGS. You said something a little bit earlier that I found interesting and actually it's what sparked my question. You had said that you don't think that they ever reported certain things to the FDA, is that right?

Dr. VUKOV. Well, if they—they claimed to every Federal—every State agency that she was not a research subject. The moment she died she was not a research subject. So then they don't have to report it to the—I would think that they don't have to report it to the FDA then. If in their head they make her a non-subject, then she's not under their jurisdiction. Their grant is saved.

Mr. CUMMINGS. Now, so, you're saying that the funding, well, like a drug study, comes from the FDA or does—I mean, where does a drug company play a role in all of that? I'm just curious.

Dr. VUKOV. Well, for a new clinic—for a clinical trial on a new drug study—this was a new drug that hadn't been OKed by the FDA. The FDA has to be involved because it's an experimental drug——

Mr. CUMMINGS. OK.

Dr. VUKOV [continuing]. That she was supposed to get, but she never got. So that's where they're at. I mean, they're the ones that—they've set up the guidelines; there are the Federal guidelines; there are the State guidelines, and they seem to match to me. So they should be thoroughly involved, and especially when there's a major issue like death.

Mr. CUMMINGS. Thank you very much. I see my time is up.

Mr. BURTON. Mr. Cox.

Mr. COX. Thank you.

Dr. Vukov, I, too, extend my sincerest apologies for all that you've been through to the extent that the Federal Government in any way contributed to it. I agree with my colleague from Baltimore; I can't think of anything worse for a parent. And I appreciate your willingness to come here and tell your story and assist us in our oversight capacity in Congress.

You indicated in your testimony that you requested help from the FDA, that you requested a review of Abby's research experience, that you went further and asked them to place a moratorium on all research involving human psychiatric subjects at UCLA, the Veterans Administration, and Jansenn Pharmaceuticals until that

investigation had taken place. On the minimal request for review of Abby's case, what was the FDA response?

Dr. VUKOV. A phone call.

Mr. COX. What happened in that phone call?

Dr. VUKOV. Well, he said, "Doctor"—I think it was Dr. Robert Johnson; he said that he just wanted me to know that he was—hadn't forgotten about me. That was it.

Mr. COX. Was there any followup beyond that?

Dr. VUKOV. I have no idea. I also wrote to OPRR 2 years ago, or maybe 3 years ago now—Office for Protection from Research Risks—and they sent me a letter saying that—outlining how you can tell when somebody's in research in the Code of Federal Regulations, and that if they adjusted your medication for purposes of research, she was in the research. But then, that was it. And then they called, or I called them, and they said that they couldn't—the person charged with doing the investigation had a relative on the IRB at Friends West. So they had to wait until there was somebody new. And then the new person called and said that, "Well, the new person was pregnant and left, and then another new person came along, and that one had surgery," and that's the last I heard.

Mr. COX. Mrs. Foster and Mr. Foster, if I could join my colleagues on both sides of the aisle here also in telling you how sorry I am at what has befallen both of you and the rest of your family. And I'm sorry, too, that so much of this seems to be not only something that involves the Federal Government, but going on in southern California at UCLA, in your case, Anaheim. That is obviously circumstantial, but it makes me even more connected to what's going on here.

You stated in your testimony, Mrs. Foster, that, quote, "The Food and Drug Administration has refused to provide documents of any type relative to this FDA-approved study," and I take it you mean they've refused to provide that to you.

Mrs. FOSTER. Yes.

Mr. COX. Notwithstanding that, you'd made a Freedom of Information Act request for that information. Can you elaborate? Has the FDA provided you with anything at all in response to your request for information about this study?

Mrs. FOSTER. I'm not certain. The last I heard, they had not. Let me just check.

Mr. COX. And how long have you been seeking this information?

Mrs. FOSTER. Six months.

Mr. COX. Oh, and I'm sure you've had a chance at some point over the years to talk to legal counsel about this issue. First of all, is that assumption correct?

Mrs. FOSTER. Yes, that's true.

Mr. COX. Have they told you whether there is any putative legal basis upon which the FDA would deny you this information?

Mrs. FOSTER. No, they haven't made that clear.

Mr. COX. Have you had a chance to hear, as Dr. Vukov did, from the FDA by telephone? Have they called you up to tell you their concerns?

Mrs. FOSTER. No.

Mr. COX. Have you called them?

Mrs. FOSTER. I have not, no.

Mr. COX. OK. Let me ask another question on the same subject. Dr. Vukov, you stated that, in your testimony, "the head of the team," without identifying the head of the team, when asked if he kept reports about Abby's death said, quote, "If I saved all the material that came across my desk, there wouldn't be any room for me to sit down." Is that Dr. Liberman?

Dr. VUKOV. Yes.

Mr. COX. And I take it that your request of him not only at that moment, but forever after, has gone unrequited. He has not answered your request?

Dr. VUKOV. This was in deposition for the medical malpractice case and—against the Emergency Room and the Urgent Care. Nobody would sue the drug company. He indicated that he didn't remember the names of the agencies that had sent the reports to him that he had read and then destroyed. So, that was the end of it. We've got that on tape, by the way.

Mr. COX. Mr. Chairman, could I have unanimous consent to ask another question?

Mr. BURTON. You got it.

Mr. COX. Mrs. Foster, you just testified that you and your husband relied upon the reputation and integrity of the Food and Drug Administration in agreeing to the test. If the Food and Drug Administration had not been involved, what might you have done differently? If you hadn't thought this was a federally supervised enterprise, what precautions might you have taken that you didn't take?

Mrs. FOSTER. You know, it's difficult to say that now knowing what I know. I hope I would have turned around and walked out. But when you see that the Federal Government is involved in something, you tend to trust. I mean, that's the way I grew up, trusting the Government. I was an Army brat and my entire life was governed by the Federal Government. And so, when I saw FDA, I knew that they approve drugs and disapprove drugs and this was a good thing. This was not something I was concerned about.

Mr. COX. And is it safe to say that you thought of FDA as a brandname, sort of like Bristol Myers, and you trusted it?

Mrs. FOSTER. No, I thought of the FDA as part of my Government that looked out for me.

Mr. COX. So even stronger than a brand name like Bristol Myers?

Mrs. FOSTER. Oh, absolutely.

Mr. COX. And as a result, you were not as cautious as otherwise you might have been?

Mrs. FOSTER. I think that's perfectly true.

Mr. COX. I thank you, and I thank the chairman.

Mr. BURTON. Thank you, Mr. Cox.

I really appreciate all of you coming in. It's always sad to hear the tragedies that people encounter; I'm sure the people at the FDA

feel empathy for the tragedy that has befallen you. What we're trying to do is find out why it happened, to try to make sure that those sorts of things don't happen in the future. So, Dr. Vukov, we appreciate your being here.

Dr. VUKOV. Thank you.

Mr. BURTON. And Mrs. Foster and Mr. Foster, we appreciate your being here.

[The information referred to follows:]

[redacted]

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May 18, 1998

Representative Burton
Chairman
Government Reform and Oversight Committee
2157 Rayburn HOB
Washington, D.C. 20515

Dear Representative Burton:

Thank you for inviting me to participate in the hearing entitled Clinical Trial Subjects: Adequate FDA Protections. I would like to take this opportunity to more clearly summarize my testimony presented at the hearing and discuss ways to improve the safety of human subjects in this country.

(1) My daughter's case was pivotal in the Los Angeles County Department of Mental Health decision to stop participation of all Los Angeles County conservatees in research of any kind.

(2) Dr. Robert Liberman 's FDA- approved research, Risperdal versus Haloperidol at Camarillo State Hospital in July, August and September 1993, violated state and federal law.

(3) According to the web site for The National Institute of Mental Health, Dr. Liberman has continued to receive at least 1.3 million dollars in grant money from the NIMH each year since my daughter died.

(4) My daughter was not considered suicidal by any psychiatrist before she entered the UCLA/Camarillo Research program at Camarillo State Hospital.

(5) Under oath, Dr. Liberman admitted that he discarded agency reports and memos regarding my daughter's death indicating to me and others that he has no interest in preventing future tragedies or investigating their part in this tragedy.

(6) Dr. Liberman's group and other responsible California parties continue to deny that my daughter was a research subject at the time of her death. They have, it seems, reinterpreted the Code of Federal Regulations regarding the identification and protection of human subjects.

(7) The summer before my daughter died Dr. Liberman's research group was cited by OPRR for defective Informed Consents. I believe we were provided with similar ones for the Risperdal versus Haloperidol research.

(8) To date, I have been given only six pages of research records most of which were almost blank regarding my daughter. These records should be available for investigation when a tragedy occurs The hiding or possibly destruction of the records only serves to further illustrate how the refused to cooperate in my personal investigation and in the legal investigation of why and how my daughter died.

In summary, the rules and regulations for protection of human subjects seem to be adequate, however, if they are not enforced, they are useless and the subjects go without protection. In my daughter's case it appears that only LA County Department of Mental Health was the only government agency that issued an appropriate response to the information uncovered by myself and others including the California Depart of Health Services.

It is imperative that the federal government enforce the Code of Federal Regulations regarding human subjects. I would suggest again that when a tragedy occurs (1) all federal grants which support the research be immediately withdrawn, (2) that the involved state and the research groups be subjected to intense scrutiny by an impartial board, not an IRB, (3) that when evidence of fraud is found that the federal government should sue the sponsors and the researchers, (4) that the federal government establish means to insure that the regulations are being carefully followed such as demanding that each subject 's life be insured for $250, 000.00 (5) that the federal regulations be rewritten to include oversight by an internist not employed by the sponsors or the researchers and (6) and that private lawyers be encouraged to sue for the subject and /or the family.

It is now obvious that the disregard for human life is spilling over into the non-psychiatric community. I beseech you to consider my recommendations and respond to the needs of us all.

I would appreciate it if you would include this letter in the Congressional Record with my testimony to the subcommittee.

Sincerely

Judith Vukov, MD

Mr. BURTON. And with that, we'll bring our next panel up. Our next panel is Dr. Peter Lurie and Dr. Adil—I hope I pronounce this right—Adil Shamoo. Is that correct? Please approach the table. Would you both rise please?

[Witnesses sworn.]

Mr. BURTON. I think we'll start with you, Dr. Shamoo. You want to make an opening statement?

STATEMENTS OF ADIL E. SHAMOO, RESEARCH SCIENTIST, REPRESENTING CITIZENS FOR RESPONSIBLE CARE IN PSYCHIATRY AND RESEARCH; AND PETER LURIE, M.D., PUBLIC CITIZEN'S HEALTH RESEARCH GROUP, AND INSTITUTE FOR SOCIAL RESEARCH, UNIVERSITY OF MICHIGAN

Mr.SHAMOO. Yes. Thank you, Mr. Chairman. I'm Adil E. Shamoo from Columbia, MD. I'm here today to speak on behalf of thousands of vulnerable patients and their families not able or not willing to speak for themselves. I'm here to speak on behalf of Citizens for Responsible Care in Psychiatry and Research. As has been mentioned, it was our organization which unearthed the use of fenfluramine on unsuspecting children in New York.

For the purpose of identification only, the following is a brief statement about my background and my involvement in this area. I'm a professor and former chairman of the Department of Biochemistry and Molecular Biology at the University of Maryland's School of Medicine in Baltimore, MD. For the past 10 years, I have been writing and speaking extensively on issues of ethics in research. I am the editor-in-chief of the journal, "Accountability in Research," and have chaired five international conferences in the subject, with a sixth one next November.

I would like to thank you, Mr. Chairman, and members of your committee, for giving me this opportunity to inform you of my personal and my organization's grave concerns regarding the current ongoing research practices of using vulnerable human beings such as the mentally ill and children as human patients/subjects in high-risk experiments on placebo which cause them harm.

Let me state at the outset that we support research with human subjects, but only if their basic human rights are fully respected. Mentally disabled individuals should only be used as research subjects when it's in their best medical interest. Only under extreme, unique, and rare circumstances should this population be used for research without direct medical benefit to them, and only when there is minimal risk involved.

Currently, uncomprehending patients and children are at the mercy of over-zealous psychiatric researchers who claim a "moral imperative" to conduct high-risk, painful experiments on the mentally ill in the name of science. The attitude of current psychiatric researchers is not different from those who conducted the Tuskegee study. As shocking as it may sound, researchers believe individual subjects of research must be sacrificed for knowledge that will help future generations.

The Minneapolis cases—allow me to give you an example of the neglect that occurs in the research on the mentally ill. Imagine If your daughter or sister or mother, who was known for 15 years to be suicidal, described to her caregivers exactly how she planned to

commit suicide. Imagine that you learned she had repeatedly stated that she would commit suicide by jumping off a downtown bridge. Then imagine that your loved one was enrolled in a "washout" clinical trial for a new drug, Sertindole, to be a part of an FDA drug approval submission. She was enrolled in this study, which violated the terms of the protocol which states those who are suicidal are excluded. She was not monitored by the researchers and proceeded to commit suicide by jumping off the very bridge that she identified to her caregivers. This happened in Minnesota just a few years ago, along with a second suicide, in a study that was regulated by the Food and Drug Administration.

Testimonies of patients and their families—on September 18, 1997, patients and families testified before the National Bioethics Advisory Commission, NBAC, that they are victims of therapeutic neglect, betrayal of trust, and institutional deception. The patients endured horrendous treatment in ill-conceived, highly speculative, dangerous experiments which clearly undermined the best medical interest of the subjects, often causing them profound harm.

Mr. Chairman, many of these experiments are authorized and condoned by the FDA and not properly monitored by that agency or any other that has jurisdiction. These living witnesses represent countless others who have also been harmed and abused in experimental research but who remain silent. The families and patients testified that drug washouts and placebo experiments were conducted without disclosure of known risks, in other words, without informed consent.

One, consent forms were often presented to subjects who could not understand them, and often presented after the experiments were already underway.

Two, patient records were deliberately changed to fit experimental protocols.

Three, patients' medical and psychiatric conditions were allowed to deteriorate severely.

Four, patients were subjected to illegal use of restraints.

Five, patients were assaulted and injured by staff.

Six, experimental drug withdrawal procedures led to a suicide attempt.

Seven, one patient on a locked research ward was impregnated and then driven quickly to a clinic outside the institution to obtain an abortion.

I believe this issue is of greater magnitude than the two well-known instances in our recent history—namely, the Tuskegee syphilis and the radiation exposure experiments.

First, the sheer number of mentally-disabled victims who have been used in recent years without their informed consent surpasses the number of those who were victimized in the Tuskegee syphilis and the radiation exposure experiments.

Second, unethical experiments with vulnerable, mentally-disabled human beings are being conducted now, as I speak to you. Mr. Chairman, when patients are taken off psychotropic medication to determine whether an investigational drug would be of benefit, their suffering is substantially greater than that of most other patients. We need to find a better way to obtain these patients' in-

formed consent. This question is critical, because it is the patients' capacity for self-determination that is affected by their illness.

When medications are abruptly withdrawn in a research protocol, the relapse rate is as high as 80 percent. When is the risk to patients considered a sufficient deterrent to the researcher or to the Institutional Review Boards which routinely approve such protocols? A schizophrenia relapse has serious, lasting, harmful consequences for the patient. It can even be life-threatening.

Mr. Chairman, scientists know that in any study there are dropouts, people who suffer consequences of the study and quit. Thus, it is particularly disturbing that in 88 percent of the studies we looked at, the researcher failed to report any dropouts during research and those that mention dropouts do not indicate the outcome or whereabouts of these human subjects.

Although the suicide rate among individuals with schizophrenia is very high, 1 percent per year, according to NIMH, we discovered that not a single suicide was reported in 41 U.S. studies of thousands of patients over the past 30 years. This is in contrast to patients' and families' recent testimonies that I just cited. This, of course, raises not only ethical concerns that patients have attempted or succeeded to commit suicide which has never been reported, but it also raises the issue of the integrity of the research data reported. Were these suicides or attempted suicides ever reported to IRB's and other officials as required by the regulations? Why have FDA and OPRR not investigated unreported suicides and attempted suicides?

To illustrate how out-of-touch the psychiatric community is with the abuses that they are committing, I will read a quote from a recent article in their literature. And I quote: Twenty-eight acutely psychotic patients with schizophrenia were recruited. All of the patients in this study were capable of informed consent and entered voluntarily, end of quote. Mr. Chairman, a statement like this is counter-intuitive and plainly absurd.

There is a belief among researchers that drug washout periods and placebo controls were mandated by the Food and Drug Administration in drug trial studies. The FDA may come here today and tell this committee that placebo-controlled trials are not required by FDA. But as a matter of standard practice, FDA officials, and especially Dr. Temple behind me, publish and speak to the scientific community and strongly suggest the need for placebo-controlled studies, as well as washout periods where patients are taken off their medication.

Drug companies who invest billions of dollars in research every year know to listen to what Dr. Temple and his colleagues are telling them if they want their drugs to be approved. And these drug sponsors will continue to design trials with placebo arms that cause undue risk to patients until the FDA changes its approach. By influencing this unethical research, FDA has gone far beyond its mandate and is promoting continued suffering among clinical trial subjects.

Recommendations: Mr. Chairman, the exploitation of uncomprehending, mentally-disabled patients in high-risk, nontherapeutic research which offers no direct benefit to its subjects is a violation of fundamental human rights. In order to promote the

ethical use of vulnerable subjects in research, we offer the following recommendations.

One, call for a moratorium of all non-therapeutic, high-risk experimentation with placebo control with vulnerable populations and children which is likely to cause a relapse. Drug wash-out and chemically induced relapse studies should be outlawed.

Two, all research trials involving human subjects should have independent oversight.

Three, full disclosure of risks must be enforced.

Four, a statutory mandate requiring that all adverse consequences suffered by human subjects during any part of a clinical trial, including the initial washout phase, should be immediately reported to the FDA or other appropriate regulatory agency.

In closing, we ask the committee to investigate the unethical exploitation of vulnerable human beings, especially children, who cannot give informed, voluntary, or comprehending consent, who are, nevertheless, subjected to experimental research studies and on placebo which are against their own best interests. We believe that such experiments on non-consensual persons violate fundamental human rights. And I thank you, Mr. Chairman.

[The prepared statement of Mr. Shamoo follows:]

I am Adil E. Shamoo from Columbia, Maryland. I am here today to speak on behalf of thousands of vulnerable patients and their families not able or not willing to speak for themselves. I am here to speak on behalf of Citizens for Responsible Care in Psychiatry and Research. For the purpose of identification only, the following is a brief statement about my background and my involvement in this area.

I am a professor and former chairman of the Department of Biochemistry and Molecular Biology at the University of Maryland, School of Medicine in Baltimore, Maryland. For the past ten years, I have been writing and speaking extensively on issues of ethics in research. I am the editor-in-chief of the journal Accountability in Research.

I have chaired five international conferences in the United States and in Europe on issues of Ethics in Research. The last such conference I chaired was on January, 1995 on "Ethics in Neurobiological Research with Human Subjects." The conference consisted of 43 scholars in ethics, psychiatric research, human rights, and advocacy. The conference proceeding is now in print. For the past two years, I have been serving as a member of the "Research Working Group" appointed by the Maryland Attorney General's Office to propose legislation extending health care decisions Act to research subjects. My comments are based on analysis of tens of research studies published in the past thirty years in various journals worldwide with special attention to those conducted in the U.S.

I would like to thank you Mr. Chairman and members of your Committee for giving me this opportunity to inform you of my personal and my organizations grave concerns regarding the current ongoing research practices of using vulnerable human beings such as the mentally ill as human patients/subjects in high risk experiments on placebo which cause them harm.

Let me state at the outset that we support the use of human subjects in research, but only if their basic human rights are fully respected.

The basic principle ought to be that individuals should only be used as research subjects when it is in their best medical interests. Only under extreme, unique and rare circumstances should we use this population for research without direct medical benefit to them. We should not design disguises such as advance directives in order to use people in research especially vulnerable subjects such as the mentally ill. The only exception that can be made is for minimal risk research with such population. Therefore, we call for:

1. An immediate moratorium on all non-therapeutic high risk experimentation with vulnerable population which may exacerbate their illness. This moratorium should include: medication washout, placebo controls, and the use of chemicals such as amphetamine and cocaine known to induce relapse with severe symptoms such as psychosis and delusions.

2. A full and thorough investigation of the past thirty years of neuropsychiatric research experiments that were of high risk and may have harmed patients.

This is important because of the high risk to uncomprehending patients who are currently at the mercy of over zealous psychiatric researchers who claim a "moral imperative" to conduct high risk, painful experiments on uncomprehending patients, in the name of "science" (Lehrman/Sharav, 1997). The attitude of current psychiatric researchers is no different from those who conducted the Tuskegee study– they believe individual subjects of research must assume risks (i.e., be sacrificed) for knowledge that will help future generations.

The issue we bring to you, I believe, is of greater magnitude than the two well known instances in our recent history –namely, the Tuskegee Syphilis study and the radiation exposure experiments. I say this for the following reasons:

(1) The sheer number of mentally disabled victims who have been used in recent years without their ability to comprehend the nature of these invasive, high risk, often painful experiments, and who could not, therefore, give their informed consent, surpasses the number of those who were victimized in the Tuskegee Syphilis and radiation exposure experiments (Katz, 1972, ACHRE, 1995).

(2) Unethical experiments with vulnerable, mentally disabled human beings are being conducted now, as I speak.

The importance of this issue I bring before you was highlighted in recent published letter by Edmund G. Howe, M.D., J.D., and Editor-in-Chief of The Journal of Clinical Ethics. In his letter, Howe says:

"I consider the problems he addresses [referring to me] *regarding research involving patients with mental illness, and particularly those with schizophrenia, among the most important in medical ethics. The first problem his study highlights is when--if ever--these patients should be taken off psychotropic medication or have it reduced to determine whether an investigational drug would be of greater benefit. This question is extraordinarily important because whenever these patients become ill--as a result of their medication being withdrawn or of its not being effective--their suffering is greater, and substantially greater, than that of most other patients. The second problem highlighted is the need to find the best way to obtain these patients' informed consent. This question is critical, because it is the patients' capacity for self-determination that is affected by their illnesses."*

<u>Brief Historical Perspective</u>

Modern historians now agree that the atrocities committed during the Nazi era in Germany, occurred because thousands of individuals collaborated and willingly carried out the Nazi mission. Among them were a large number of academicians, scientific researchers, and physicians who provided the Nazi regime with the technology and the pseudo-intellectual ideological justification for the most barbarous acts against human

victims, such as the mentally ill (for reviews see, Caplan, 1992, Muller-Hill, 1988, Proctor, 1988, Shamoo and O'Sullivan, 1997).

The most troubling question that continues to perplex us all is how to ensure that our fundamental moral principles are not compromised in the name of science, and how to ensure that the human rights of the most vulnerable disabled individuals who are unable to protect themselves, are not violated for the convenience of society or, more likely, for those who are in a position of power.

We are cognizant of the difference in degree between contemporary psychopharmacologists who conduct high risk drug-trial experiments on vulnerable mentally disabled persons who are unable to give informed consent – thereby violating their human rights--and the crimes against humanity which were condoned and carried out by tens of thousand of German physicians, nurses, and health care providers—all of whom had been educated in professional schools where they were taught to heal the sick.

Code of Ethics

Following the revelations of the Nazi biomedical atrocities, in 1946, the American Medical Association adopted three requirements for experiments using human subjects – voluntary consent, prior animal experimentation, and proper medical protection. Following the Nuremberg trials of German medical researchers, the world community adopted the "Nuremberg Code" in 1947 as the universal ethical standard for the entire civilized world (cited in ACHRE, 1995, p. 103). The civilized world tried and convicted those who conducted such research experiments on human subjects. Also, the civilized world tried and convicted the Nazi doctors for conducting experiments on non-consenting human subjects which , while in-part, technically legal under Nazi laws, violated basic universal human rights and constituted "Crimes Against Humanity " (Shamoo and O'Sullivan, 1997).

Three basic inviolable requirements for ethical research with human subjects under Nuremberg are: (1) lack of "coercion" and "duress", (2) sufficient knowledge, and (3) comprehension. These requirements are the essence of what subsequently became known as "Informed Consent." The Declaration of Helsinki (1964) augmented the Nuremberg code by introducing the concept of "direct therapeutic benefit" and that the person must be legally competent to give consent. The Declaration of Helsinki also state that "the interest of science should never supersede the interest of patient"
(WMA, 1964).

Informed Consent

The consent of individuals to undergo any experimentation on their person has been recognized in principle throughout the Judeu-Graeco-Roman-Christian and Islamic code of ethics. Our American founding fathers , most notably Jefferson, recognized that governing individuals (let alone experimenting on them) cannot and should not be done without the consent of the governed.

Despite this rich history in Western culture, despite the adoption of formal codes and declarations, it is distressing to learn that though the public assumes that medical researchers respect the rights of their human subjects, this is not universally practiced in this country. In his landmark article " Ethics in Clinical Research ", Henry K. Beecher described fifty American medical experiments which violated ethical standards. Similarly, Jay Katz's anthology (1972) described numerous cases obtained from published literature and court cases of consistent disregard for the rights of patients - subject by the physician/investigator.

The Tuskegee Syphilis study conducted between 1930's - 1970's in which researchers allowed 400 African-American men to suffer from the natural course of syphilis (cited in ACHRE, 1995, p. 178). Even after penicillin became available in the 1940's, it was withheld and the experiment continued so as to allow the researchers to witness the natural course of syphilis. The Tuskegee revelations outraged the American public. Its outcry led Congress to create in 1974 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission's recommendations are embodied in the " Belmont Report, " the foundation for American ethical standards in research with human subjects. In all, there have been three (excluding this one) National Commissions resulting in the enactment of several laws regulating research with human subjects known as "Common Rule" (for review see ACHRE, 1995).

The Belmont Report recognized the vulnerability of the mentally ill, it stated, " given their dependent status and their frequently compromised capacity for free consent, they should be protected." Eventhough the subsequent laws did not mention the "mentally disabled" by name, it clearly indicated that any vulnerable group needs special protections and a second level of review beyond the IRB should be utilized (Shamoo and Irving, 1993). In its 1993 Guidelines, federal OPRR clearly recognized the need for additional safeguards *"protects the rights and welfare of these subjects "*--you can set the wheels in motion to fulfill that urgent need.

In all ethics codes, declarations, and regulations, three crucial elements of informed consent must be observed -- lack of duress and coercion, sufficient knowledge, and comprehension. Having studied and surveyed the published literature on specific types of schizophrenia experimental research for the last thirty years, I will demonstrate to you that one or more of these cardinal rules were violated in experiments involving patients diagnosed with schizophrenia.

<u>High Risk and Unethical Research with Placebo Protocol</u>

Mentally disabled human beings are currently at high risk of becoming subjects of unethical, invasive non-therapeutic experiments which abruptly interrupt treatment, on placebo destabilize their condition. In some experiments, patients are injected with symptom inducing chemicals such as L-dopa, amphetamines, PCP, apomorphine and compounds shown to be carcinogenic in animal studies (Shamoo and Keay, 1996, Lehrman, N. S. and Sharav, V. H. , 1997).

Two recent studies, one ours and another by four San Diego researchers led by P. L. Gilbert, surveyed literature for the past three decades of studies involving complete sudden withdrawal of medication from patients (washout) with subsequent return of symptoms of psychosis and delusions (relapse). These experiments involved 4,365 patients diagnosed with schizophrenia (Shamoo and Keay, 1996, Gilbert et al., 1995). In 1983, the leading psychiatric researcher's (Schooler and Levine, 1983) own words best describe these experiments: "*In the typical design, patients were randomly withdrawn from their ongoing medication to either a standard drug or to a placebo so that the treatment was double blind. Whether or not the patient relapsed and how long it took until relapse, were the reported outcomes....Typically the withdrawal studies were of longer duration, three, four, or even nine months...*".

To gain insight into the painful human consequences of such drug-free experiments we must listen to the testimony of human subjects and their families (see the special ETHICS issue of The Journal of the CAMI, ed. Sharav, 1994, Becker, 1994, Aller and Aller, 1996).

One of the key finding of our own paper was that 39% of patients in such studies in the U.S. undergoes a relapse (Shamoo and Keay, 1996). This rate is rather modest when compared to the larger study of Gilbert et al (1995) which found 53% of the patients withdrawn from medication to have endured a relapse as compared to 16% of those patients who remained on their medications. A schizophrenia relapse has serious, lasting, harmful consequences for the patient, it can even be life-threatening. When medications are withdrawn, the relapse rate is as high as 80% (Shamoo and Keay, 1996, Gilbert et al., 1995) --when is the risk to patients considered a sufficient deterrent to the researcher or to the Institutional Review Boards which routinely approve such protocols?

In our survey of U.S. studies, we found that in 56% of patients enrolled there is no mention of informed consent and that only 32% of patients signed consent forms. In 39 out of 41 studies, the reports neither mention as to whether the patients comprehended the risks/benefits of enrolling in a research protocol nor used comprehension as an inclusion/exclusion criteria for enrollment. The researchers' inattention to the patients' ability (or lack thereof) to comprehend the risks involved is especially troubling considering the fact that these subjects were persons suffering from schizophrenia -- the severest form of mental illness -- and the fact that federal regulations require that all those signing informed consent should have the capacity to comprehend what they have signed. Perhaps even more disturbing, is the fact that 88% of these studies the researcher failed to report any dropouts from the research protocols, and those that mention dropouts do not indicate the outcome or whereabouts of these subjects.

In the GAO report of March, 1996, they cite FDA letters to industry that states:

"These letters cited instances of serious misconduct, including failure to obtain informed consent; forgery of subject's signatures on informed consent forms; failure to informed patients that a drug was experimental; fabrication of data to make subjects

eligible for study; submission of false electrocardiograms. X rays, and lab test results to the company underwriting the research; failure to report subjects' adverse reactions to drugs under study, including a subject's death; failure to obtain informed consent and an IRB's approval for a study touting a human growth hormone as a cure for Alzheimer's disease; proceeding with a cancer study after FDA had suspended it for protocol deficiencies; and failure to inform patients that a drug sold to them was experimental and contained a steroid."

In a leading psychiatric research journal, Carpenter, Schooler, and Kane in (1997, p. 403) admit:

"The risks associated with medication-free periods include the prolongation or the re-emergence of psychosis. If careful supervision is not in effect, or if severe exacerbation are not treated appropriately, subjects may be at risk for loss of judgment and insight, personal harm or harm to others, job or housing loss, increased burden to family or other caregivers, or other complications of psychosis."

They further acknowledge that *"These risks are known and current studies must include safeguards to reduce such serious risks."*

However, in their abstract they stated:

"A radical revision of procedures for research review and implementation is not indicated," (Carpenter, Schooler, and Kane, 1997, p. 401)

They go on to say:

"We also remind the reader that no evidence of any widespread ethical problem in schizophrenia research has been presented and no indication that research participants have an adverse long-term course of illness has been forthcoming," (Carpenter, Schooler, and Kane 1997, p. 406)

Another important piece of survey data we discovered was that not a single suicide was reported in the entire 41 US studies of thousands of patients for the past thirty years (Shamoo et al., 1997). This strange fact is in contrast to patients' and families recent testimonies that I just cited and the well known fact that suicides among individuals with schizophrenia is very high, circa 1% per year. We calculated that the probability that the number of suicides in all of these US studies is zero as compared to British studies is 1:500, a vanishingly small probability (Shamoo et al., 1997). This of course raises, not only ethical concerns that patients have attempted or succeeded in a suicide and never been reported but it also raises the issue of the integrity of the research data reported. Why the suicides were never reported in literature as research outcome? Were these suicides or attempted suicides ever reported to IRB's and other officials as required by the regulations. Why OPRR has not monitored these reported suicides and attempted suicides?

Jurrit Bergsma (1997) a psychotherapist and a member of an IRB in a response to our survey paper said in Cambridge Quarterly of Health Care Ethics:

"Research protocols as mentioned by Shamoo and Keay, in which medication is withheld for several months, seem to be outdated and almost comparable with programs of torture devoid of any scientific meaning. A physician who accepts real responsibility for the patient would never allow a researcher to execute such a study."

The routine inclusion of uncomprehending mentally disabled patients in high risk, non-therapeutic research which offers no direct benefit to its subjects, and half of them on placebo is a violation of fundamental human rights. In New York, the courts have recently come down hard on the states' psychiatric research policy. In a unanimous decision by a panel of five judges in NYS Sup Ct, Ap Div, the court declared that the state violated state and federal constitutions by conducting such non-consensual experiments on children and mentally incapacitated adults: *"....the controversy has wide significance since it arises within the larger context...medical research involving human subjects necessarily requires a balancing of this State's responsibility to protect individuals who, because of mental illness, age, birth defect, other disease or some combination of these factors, are incapable of speaking for themselves, from needless pain, indignity and abuse..."* (T.D. vs NYSOMH, 1996, p. 5).

The risks associated with washout/withdrawal with the use of placebo were mentioned as early as 1986: (1) seven times more criminal activities; (2) increased bizarre behaviors which stigmatizes the patient further (3) increased morbidity; (4) psychosis which by itself maybe toxic; and (5) delayed intervention resulting in poor long-term outcome (Wyatt, 1995). Gilbert et al., (1995) and Jeste et al., (1995) have cited that slow tapering off reduction of medication over six months resulted in 8% relapse rate whereas rapid reduction of medication resulted in 50% relapse rate.

In 1997, a published report of a federally funded experiment conducted at New York State Psychiatric Institute, fenfluramine (Pine et al., 1997) was infused into 34, 6- to 12 years old, I repeat 34, 6- 12 year old inner city, minority boys of whom 44 percent were African Americans and 56 percent Hispanic. The dubious purpose of this experiment in which the subjects were innocent brothers of convicted felons—they have no illness, they have no disease—was to prove that, and I quote from their paper, "biological factors, abnormalities in the serotonergic nerve system" predispose them to aggressive behavior. This experiment was conducted by the Department of Child and Adolescent Psychiatry and Biological Study Unit of New York's premier psychiatric research center. Similar experiments with fenfluramine are also reported in the literature. Between 1990-1997 FDA received adverse reports from using fen-fen of which fenfluramine is the active ingredient, of 70 deaths and 545 symptoms of heart and lung damage (Kerr, 1998). FDA should either have pulled the drug from the market or warned the physicians of the serious side effects. FDA's action would have removed the last fig-leaf the researchers use as an excuse to inject those youngsters with fenfluramine. The fact remains that the use of fenfluramine on these

children was not indicated and it was not for their medical benefit. They were use merely as experimental subject- i.e. as guinea-pigs.

The Minneapolis Cases

A patient known for 15 years to be suicidal and describes to her care givers exactly how she will commit suicide. The patient repeatedly stated that she would commit suicide by jumping off a downtown bridge. The patient was enrolled in a washout clinical trial for new drug Sertindole to be a part of an FDA drug approval submission. The patient was enrolled in a study with placebo control for the new drug violating the exclusion criteria of the protocol. She proceeded to commit suicide in the exact same manner as she described. Another patient was discharged after refusal to enroll in such studies and also committed suicide (Roe, 1998).

Testimonies of Patients and their Families

On September 18, 1997, patients and families testified before the National Bioethics Advisory Commission (NBAC) that they are victims of therapeutic neglect, betrayal of trust and institutional deception. The ordeals the patients endured in ill-conceived, but peer-approved, highly speculative, relapse-producing experiments clearly undermined the best medical interest of the subjects, often causing them profound harm. These living witnesses represent countless others who have also been harmed and abused in experimental research but who remain silent. The families and patients testified that experiments with large numbers on placebo were conducted without disclosure of known risks, hence without informed consent: (1) Consent forms were often presented "en masse" to subjects who were unable to comprehend them, and were often presented after the experiments were under way. (2) Exclusion criteria of protocols were violated. (3) Diagnoses were altered to fit the experimental protocols. (4) Patient-subjects' medical and psychiatric conditions were allowed to deteriorate severely without intervention. (5) Several of these patients were subjected to illegal use of restraints. (6) Several patient-subjects were assaulted and injured by staff. (7) A patient on a locked research ward was impregnated and (8) Experimental drug withdrawal procedures led to a suicide attempt.

Some of the patients testimonies even though not current, the abusive practices are current and on-going as I speak to you now.

Informed Consent and Comprehension

The researchers own methodology statements in the studies we surveyed indicates that no attempt had been made to ensure that cognitively impaired, delusional patients were excluded from these high risk, non-therapeutic experiments because of their inability to comprehend. The psychiatric community's blind eye and deaf ear to ethical violations by its members is apparent in the professional literature where investigators seem oblivious to the contradiction of their statements when they report : *"Twenty-eight acutely psychotic patients with schizophrenia* [were the

subjects]." *"All of the patients in this study were capable of informed consent and entered voluntarily."* (Barbee et al, 1992).

Institutional Review Boards and Research with the Mentally Disabled

Federal "Common Rule" authorized the creation of local Institutional Review Boards" (IRBs) to pass judgment on proposed research using human subjects. However, local IRBs are composed mostly of researchers representing the interests of, and primarily concerned with, scientific research rather than patient-subjects' welfare, thus it is not surprising that they have failed to safeguard the patients from drug trial studies which exacerbated painful psychotic symptoms and schizophrenia relapse. The evidence clearly confirms the need for independent oversight and enforcement mechanisms to protect vulnerable human subjects.

Immoral Experiments

The Advisory Committee on Human Radiation Experiments (ACHRE, 1995) reformulated the ethical principles of the past in using human subjects in research in a new wordings of six principles. The first of these six principles enunciated by the ACHRE is : *" one ought not to treat people as mere means to the ends of others ."*

Unfortunately, an important and powerful research organization - the American College of Neuropsychopharmacology (ACNP , 1996) whose members conduct psychiatric research with human subjects continues to upholds standards of ethics which have been rejected since Nuremberg. In their most recent statement of Principles of Ethical Conduct about the subject states :

" All persons living in society have a moral responsibility to participate in efforts to promote and contribute to the present and future welfare of that society. Research is one these obligations. "

It is especially distressing that the fraternity of psychiatric researchers in our country continues to invoke a morally unacceptable ideology to lay claim to their unsanctioned right to conduct non-therapeutic experiments on mentally disabled persons. NO ONE HAS A MORAL OBLIGATION TO PARTICIPATE IN RESEARCH -- mentally disabled persons who are incapable of making an informed, voluntary decision, should never be exploited for the benefit of others. Ethicist Tom Beauchamps' (1996, p. 264) rebuke of the human radiation experiments applies equally well to the use of the mentally disabled in research :
" Never in the history of civil medicine has it been permissible to exploit patients by using them to the end of science in non-therapeutic research that carries risk of harm. "

FDA and Placebo Controls

There is a believe among researcher that drug washout periods and placebo controls were mandated by the Food and Drug Administration (FDA) in drug trial studies.

"This is not the case. In fact, FDA regulations do not require washouts: the agency's "Clinical Guidelines" (HEW publication No. 77-3040-FDA-1978) suggests "These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigating drugs or to obtain approval of a new drug for marketing." Furthermore, the guidelines under the heading, "Procedures," states: "Prior to administration of a new drug, whenever feasible, all patients or subjects shall have been off previous drugs, including over-the-counter drugs, for at least two and preferably four weeks. In some cases where the previous drug has a prolonged duration of action, a longer washout period will be required for return to physiologic state." We should note the phrase "whenever feasible" and also on page 9 under the heading Phase One and Two Studies states: "Patients selected for early Phase Two Studies should ordinarily be free of hematologic, hepatic, renal, cardiac or other serious disease. To avoid possible interference with assessment of safety and effectiveness of the investigating drug, they should be receiving no concomitant therapy, if feasible." We should again note the phrase, "if feasible." (From Shamoo, 1994).

Recommendations

In order to promote the ethical use of vulnerable subjects in research, we offer the following recommendations:

1. Call for a moratorium on all non-therapeutic, high risk experimentation with placebo control with vulnerable populations which is likely to cause a relapse: drug washout and chemically induced relapse studies should outlawed.

2. Each participant in a research protocol should be assisted by an independent physician (not connected with the project or the institution where research is conducted) to help decide whether or not the continuation of the patient in the research protocol is in the patient's interest?

3. An independent psychiatrist should determine the capacity of potential participant to comprehend the risks and benefits of enrolling in the proposed research study.

4. Full disclosure of risks must be enforced -- including risks associated with drug withdrawal, placebo, and potential side-effects. Full disclosure of informed consent procedure and funding source should be required.

5. IRB's should reside independently of the institution where the research is conducted. The majority of IRB members should be independent of the institution where the research is conducted. The majority of IRB members should come from the community and when considering the use of vulnerable mentally disable persons, at least two patient's representative should be involved. Only a minority should come from the scientific community and/or the institution.

In closing, we ask the Committee to investigate the unethical exploitation of vulnerable human beings who cannot give informed, voluntary or comprehending consent,

who are nevertheless subjected to experimental research studies and on placebo which are against their own best interests. We believe that such experiments on non-consensual persons violate fundamental human rights.

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Mr. BURTON. Thank you, Dr. Shamoo. Dr. Lurie, you want to make an opening statement?

Dr. LURIE. Yes. Thank you for the opportunity to testify before the committee on the critical issue of inadequate protections for human subjects, specifically the use of placebos.

I think a good place to start here is with the well-known World Medical Association's Declaration of Helsinki, which states unequivocally that, quote, "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method." Now, I will refer you, too, to the Federal regulations cited here in my testimony which also seem to preclude placebo-controlled trials when an effective therapy has been identified. They say that active-controlled trials, i.e., non-placebo-controlled ones, are to be used, quote, "when the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient."

I just want to make sure that you understand, we're not objecting to the use of placebos per se. Our objection is to the use of placebos in those circumstances where there is a known effective therapy, with an arguable exception being made, perhaps, for minor conditions like mild pain. But it's the use of placebo in the circumstance when there is a known effective therapy that is, in our view, at issue here.

Now, numerous authors have catalogued large numbers of studies in various parts of medical science where placebos have been used in the aftermath of a proven therapy. I'm going to mention three newer ones. The first is in the area of treatment for hypertension, and a particular kind of hypertension known as Isolated Systolic Hypertension, where a study published in 1991, known by the acronym SHEP, showed the benefits over a placebo of treating that condition. Again, nothing wrong with that study. It was the first placebo-control trial of that condition. But subsequently, a study that was already in progress at the time, looking at the same question, also using a placebo control, continued, even though the results of the SHEP study were in.

A second example of this deals with the use of placebos in treatments for drug users, and in particular, the use of an, as yet, FDA-unapproved drug by the name of buprenorphine. There have been at least two studies now that have used placebos in assessing the effectiveness of buprenorphine in U.S. Government-funded studies. In one of these, even though the drug methadone has already been approved for the treatment of opiate addiction, nonetheless, instead of comparing buprenorphine to the known effect of treatment—methadone—people were instead comparing it in part to placebo. Sure enough, buprenorphine turned out to be better than placebo.

And even after that, another U.S. Government study comparing buprenorphine to placebo in 12 hospitals around the country had to be terminated early because the results were so striking that buprenorphine was better than nothing. Again, buprenorphine versus placebo would have been a better way to go—versus methadone would have been a better way to go.

We first became involved in this when we learned of 15 unethical studies being conducted among HIV-positive pregnant women in Africa. There already had been a well-done placebo-controlled trial

which showed that AZT reduced the transmission of HIV from mother to infant by about two-thirds. Yet, this set of 15 studies involving 17,000 women, most of them in Africa, proceeded with a placebo group again. We suggested that the way to go forward was to compare the newer version of AZT to the already proven version of AZT. But the CDC and NIH demurred and continued conducting these studies.

Well, in February of this year, the results of one of those studies was finally published. And sure enough, not to our surprise, the newer regimen turned out to be better than nothing. In fact, the transmission was reduced by 51 percent. Almost two dozen infants were unnecessarily infected with HIV during the course of this trial. Public health action was delayed for 4 years, while 500,000 infants a year became infected with HIV, primarily in developing countries, and we still don't know whether the two AZT regimens are better or worse than one another. It's not likely that the shorter one is better than the longer one. But in any event, there's been no head-to-head comparison of those things to date.

These examples indicate that the problem of the use of placebos when an effective treatment exists is not simply a violation of accepted ethical guidelines. They often do not provide the information that is most useful clinically. A drug treatment professional is not really interested in whether buprenorphine is better than nothing. They're interested in whether or not buprenorphine is as good or about as good as methadone. But placebo-control trials don't answer that question. An active-control trial in which you compare the two putative treatments, say, methadone and buprenorphine, benefit many parties. The experimental subjects, of course, benefit because they're not exposed to the placebo and its known lack of effectiveness. The doctors benefit because now, after the study is done, they're able to make a better clinical decision based on which of the drugs is actually superior. The patients benefit because their doctors can make better decisions. And those people who are paying for health care are in a better decision to select among the alternatives.

One of the things that is important here is that as medical knowledge advances, there are increasingly few conditions for which we have no treatment. And what that means, it seems to me, is that the role of active-control trials is going to be increasingly important, and the placebo-controlled trials should slowly, slowly be fading away as more and more known treatments are identified.

Between—in 1990 and 1991, the last years for which FDA collected such data, only 27 percent of the 49 new drugs approved by FDA represented, quote, "important therapeutic gains." So more and more drugs are coming on the market, where the more useful information would be how they compare with what we already have.

What is the role of FDA in all of this? Well, one reason, one problem is that the placebo-controlled trial has become a kind of religion in science. In studies with other designs, no matter how preferable they might be from an ethical or clinical or public health perspective, they are subject to criticism because they fail to live up to the so-called "gold standard"—the placebo-controlled trial.

And FDA is not the only source of this problem, but it is clear that it is a critical driving force behind the use of placebos for two reasons.

One, because the approval of medications is seen as requiring the use of a placebo control for American drug approval. And the second is because of the way the FDA is so highly regarded internationally; we create a standard that other countries copy when they decide how clinical trials should be conducted, regardless of whether FDA approval is or ever will be an issue.

Both critics and supporters of placebo-controlled trial orthodoxy point to a series of articles by Dr. Temple of FDA as evidence that the FDA heavily favors placebo-controlled trials over active-controlled ones. It's ironic, therefore, that in fact neither FDA laws nor regulations in fact require placebo-controlled trials. Rather, they require what are called "adequate and well-controlled studies." And a number of alternatives are listed, including active-control trials, one example of which might be called an "equivalency study."

So, in fact, new drugs can be approved in the absence of placebo-controlled trials, and in fact there are even some parts of FDA where almost all drug approvals are based on active-control trials or equivalency studies. Oncology, for example, as was previously hinted at, hardly ever uses placebo-controlled trials and whole parts—in the FDA there is a whole division in infectious diseases that is devoted exclusively to equivalency studies.

So clearly, the statistics are good enough to do equivalency studies. Clearly, the methodology is in place. But still, the ideology is being transmitted to American researchers and people throughout the world that the FDA has a preference for this. I list in my testimony a number of drugs that have recently been approved using equivalency studies, and so I won't repeat that.

Let me close by addressing some potential legislation that might reduce the number of placebo-controlled trials. As I mentioned, FDA appears to heavily favor placebo-controlled trials, even though their existing regulations permit them greater flexibility than they in fact exert. It's clear that the manufacturers themselves, acting in their own self-interest, do not have a very strong interest in conducting active-controlled trials, because it's an easier hoop to jump through to prove that something is better than nothing than to show that it's about as good as something already approved. And that, I think, in part, is where your committee and the Congress have potentially a role. What we have, then, is a situation where the active-controlled trial languishes as the poor cousin of the clinical trials family, despite their obvious benefits.

Now, some countries have required pharmaceutical manufacturers to go beyond the mere demonstration of safety and efficacy compared to placebo and have required, in Norway and Iceland, for example, comparative safety and efficacy information. Again, that's the information that clinicians, doctors need—and patients need.

What's needed now is legislative action by the Congress to require active-control trials when a known effective therapy exists,

with an exception, perhaps, for mild pain. In the absence of such action, the FDA will continue its role as one of the major enforcers of the placebo-control orthodoxy and subjects, patients, doctors, and insurers will continue to play the price. Thank you.

[The prepared statement of Dr. Lurie follows:]

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Inappropriate Use of Placebos in Human Experiments

Testimony before the
Committee on Government Reform and Oversight
U.S. House of Representatives

April 22, 1998

Thank you for the opportunity to testify before the committee on the critical issue of inadequate protections for human subjects in clinical trials, specifically the misuse of placebos.

The best place to begin when discussing the ethics of placebo use is with the accepted national and international ethical guidelines. The most commonly cited is the World Medical Association's Declaration of Helsinki, which states unequivocally that "In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method."[1] While a literal reading of the Declaration might suggest that this precludes placebos altogether, it is commonly assumed that an exemption exists for the use of placebos in situations where no therapy has yet been proved effective or the condition being treated is not serious or life-threatening, like mild pain. Indeed, we do not take exception to the use of placebos per se; at issue here is the use of placebos in situations where an effective treatment for a serious medical problem has already been identified.

Further support for precluding placebo-controlled trials in most cases where effective therapy exists comes from the Nuremberg Code, which holds that "The experiment should be so conducted as to avoid all unnecessary physical and mental

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[1] Declaration of Helsinki IV, 41st World Medical Assembly, Hong Kong, September 1989. In: Annas GJ, Grodin MA, eds. The Nazi doctors and the Nuremberg Code: human rights in human experimentation. New York: Oxford University Press, 1992;339-42.

suffering and injury."[2] Indeed, even federal regulations would seem to preclude placebo-controlled trials after an effective therapy has been identified. Active-controlled trials are to be used "when the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient ..."[3] These regulations apply as long as federal funds are utilized, regardless of where the research occurs.

Yet the use of placebo controls in such situations is common. Rothman and Michels have identified a large number of studies using placebos after effective treatment was identified in areas as diverse as rheumatoid arthritis, antidepressants, congestive heart failure, hypertension and onchocerciasis (river blindness).

Placebos for Patients with Hypertension

There are several more recent examples. The results of the Systolic Hypertension in the Elderly (SHEP) study, a placebo-controlled trial of isolated systolic hypertension, a condition where only systolic blood pressure (the top number) is elevated, were published in 1991.[4] The study found that treatment of this condition was superior to placebo. A then ongoing placebo-controlled trial of this condition (Syst-Eur) funded in part by Bayer, the maker of the drug being studied, was not stopped; instead recruitment continued, including patients from Eastern Europe until 4,695 subjects were recruited, half of whom received placebo.[5] In 1997 the results of the study were published, again showing treatment to be superior to placebo. A trial with a very similar design has also taken place in China (Syst-China).[6]

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[2] Trials of war criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2. Washington, DC: U.S. Government Printing Office, 1949.

[3] 21 CFR 314.26(b)(2)(iv) 1991.

[4] SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.

[5] Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997;350:757-64.

[6] Wang JG, Liu G, Wang X, et al. Long-term blood pressure control in older Chinese patients with isolated systolic hypertension: a progress report on the Syst-China trial. J Hum Hypertension 1996;10:735-42.

Although it has been known for many years that treatment with at least some antihypertensive agents can reduce mortality, the Shanghai Trial of Nifedipine in the Elderly (STONE), partly funded by Bayer, compared the antihypertensive agent nifedipine to placebo for an average of 2.5 years.[7] After studying more than 1,600 Chinese hypertensives, half of whom were randomized to placebo, nifedipine was shown to reduce the number of cardiovascular events by 59%. In all of these studies, except the original SHEP study, an ethical design would have compared the proven treatment to the experimental treatment. Despite preexisting evidence of the need to treat these hypertensive patients, hundreds were unnecessarily exposed to placebos, leading to preventable strokes and cardiac events.

Placebos for Drug Users

Another area where unethical placebo-controlled trials are common is in drug use treatment research. This is facilitated by the paucity of drug treatment facilities in this country; only 15% of drug injectors are estimated to be in treatment on any given day. Some researchers use the lack of available treatment to argue that the placebo does no harm, since the subject would not have received treatment anyway. This is sometimes referred to as the "standard of care argument." We do not believe that it is ethically acceptable to use subjects' social conditions to justify research of this type.

Buprenorphine is a drug being studied for the treatment of heroin and other opiate addiction. We have identified two studies where placebos have been administered to subjects, even though methadone was demonstrated to be effective in treating opiate addiction decades ago. In one such study, funded by the U.S. Public Health Service, a total of 150 subjects were randomized to placebo or one of two doses of buprenorphine.[8] At the midpoint of the two-week trial, the subjects were permitted to request further random assignment to a different study arm. Not surprisingly, the buprenorphine-treated patients were less likely to request random reassignment, were less likely to use illicit opioids and were more satisfied with how well their withdrawal symptoms were controlled than the patients who received placebo. More recently, a study in 12 U.S. hospitals, coordinated by the U.S. government and the buprenorphine manufacturer, Reckitt and Colman, had to be terminated prematurely when

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[7] Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). J Hypertension 1996;14:1237-45.

[8] Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. Drug Alcohol Dependence 1995;40:17-25.

buprenorphine again proved substantially superior to placebo.[9] In an ethically designed trial, buprenorphine would have been compared to methadone. Instead, the patients in these trials were unnecessarily forced to endure the extreme discomfort of heroin withdrawal.

The Role of Active-controlled Trials

These examples indicate that the problem of the use of placebos when an effective treatment for the condition exists is no. only a problem of the violation of accepted ethical guidelines. These trials often do not provide the information that is most useful clinically. A drug treatment professional, for example, is not interested in whether a new treatment is better than nothing. To optimize therapy for a patient, the physician needs to know how the new treatment compares to the older, known effective treatment. These treatments need not be exactly equal in efficacy to be useful; depending on side effect profile, patient characteristics and even cost, the physician may even select the somewhat less effective medication. But trials that compare new treatments to placebo, with predictable results, do not aid physicians in making these decisions.

Active-controlled trials, in contrast, benefit many parties. Experimental subjects benefit by being assured that everyone will receive at least arguably effective treatment. Doctors benefit by learning how competing therapies compare with one another in a controlled trial. Once the medication is approved, patients benefit because doctors can make more informed clinical choices based on the results of these studies. Payers benefit because they can use such data to favor a cheaper, yet equally effective, drug.

As medical knowledge advances, there are increasingly few conditions for which no proven therapy exists. For example, in 1990 and 1991, the last years for which the FDA collected such data, only 27% of the 49 new drugs approved by the FDA represented "important therapeutic gains," including all AIDS drugs. The market is thus being inundated with large numbers of medications that are not substantial advances on their predecessors. Indeed, some involve only minor chemical modifications on a proven medication and are thus known as "me-too" drugs. This makes the role of active-controlled trials all the more important for the future.

The Role of the FDA

If the active-controlled trial for conditions for which known therapy exists is preferable both ethically and clinically, why does the placebo-controlled trial continue to flourish? One reason is that the placebo-controlled trial has become a kind of religion

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[9] Cloud J. A way out for junkies? Time, January 19, 1998, p. 59.

in science, and studies with other designs, no matter how preferable from an ethical, clinical or public health perspective, are subject to criticism for their failure to live up to this "gold standard." While not the only source of the problem, it is clear that FDA policy is seen as a critical driving force behind the use of placebos, both because the agency often requires them for new drug approval, and because the FDA sets a standard for clinical trials that is adopted internationally, even in studies where drug approval is not an issue. Both critics and supporters of the placebo-controlled trial orthodoxy point to a series of articles by Robert Temple of the FDA as evidence that the FDA heavily favors placebo-controlled trials over active-controlled ones.[10,11,12]

It is ironic, therefore, that neither FDA laws nor regulations actually require placebo-controlled trials for drug approval. Rather, the regulations require "adequate and well-controlled studies," and list five types of acceptable studies: 1. randomized, placebo-controlled trials; 2. dose-response studies; 3. active-controlled studies; 4. no treatment concurrent controlled studies; and 5. historical controls.[13] So new drugs can be approved in the absence of placebo-controlled studies. Indeed, in some divisions of the FDA, active-controlled trials are commonly used as the basis for drug approval. The field of oncology has for years eschewed placebo controls in trials of treatments of cancers for which effective therapy exists. In the past several years, the FDA has approved a number of antibiotics based entirely on equivalency studies, a type of active-controlled trial: trovafloxacin, cefdinir and sparfloxacin. The cardiac drug reteplase was also approved based on active-controlled testing. Yet, because these are exceptions rather than the "rule," the impression persists that the FDA has a strong preference for placebo-controlled studies.

Placebos for HIV-positive Pregnant Women in Developing Countries

We first became involved in this issue when we learned of a series of 15 unethical studies being conducted in Africa and Asia among HIV-positive pregnant women. Despite a well-conducted, placebo-controlled study in which the drug AZT was

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[10] Temple R. Problems in interpreting active control equivalence trials. Accountability in Research 1996;4:267-75.

[11] Temple R. Government viewpoint of clinical trials. Drug Info J 1982;16:10-7.

[12] Temple RJ. Special study designs: early escape, enrichment, studies in non-responders. Commun Statist - Theory Meth 1994;23:499-531.

[13] 21 CFR 314.26(b)(2) (1991)

proved dramatically more effective than placebo,[14] these 15 studies involving more than 17,000 women gave at least some women placebos or other medications not proved effective. The object was to identify a less costly method of administering AZT so that it could be accessible in developing countries where the approximately $800 per course cost of AZT was out of reach. We suggested that instead of comparing the less expensive AZT treatment regimens to placebo, they could be compared to the already-proven regimen, or one resembling it. But the CDC and the NIH, which were sponsoring or conducting most of the studies, demurred and the known, effective regimen was withheld, with the loss of hundreds of infant lives. Ironically, the NIH also sponsored one active-controlled trial, but this only happened when the director of Harvard University's Institutional Review Board stood up to repeated pressure from the NIH Study Section to instead conduct a placebo-controlled trial by writing to the NIH: "The conduct of a placebo-controlled trial for AZT in pregnant women in Thailand would be unethical and unacceptable, since an active-controlled trial is feasible."[15] In contrast, the CDC conducted its own placebo-controlled trial in Thailand, and even continued it after AZT became so available in Thailand that Thai researchers canceled their own placebo-controlled trial.[16] (Incidentally, the CDC research in Thailand, as well as a companion CDC-sponsored placebo-controlled trial in Cote d'Ivoire, were conducted without the Assurances required for such international research until we criticized the studies.) [17]

The results of CDC's placebo-controlled trial in Thailand were made public in February of this year. Not surprisingly, the less expensive AZT regimen was also dramatically more effective than placebo.[18] Almost two dozen infants were unnecessarily infected with HIV during the trial, public health action was delayed four years while public health officials awaited the results of the trials as 500,000 infants per

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[14] Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. New Engl J Med 1994;331:1173-80.

[15] Brennan T. Letter to Gilbert Meier, Division of Research Ethics, NIH, December 28, 1994.

[16] Phanupak P. Ethical issues in studies in Thailand of the vertical transmission of HIV. New Engl J Med 1998;338:834-5.

[17] Shalala DE. Letter to Sidney M. Wolfe, Director, Public Citizen's Health Research Group, July 15, 1997.

[18] Centers for Disease Control and Prevention. Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission--Thailand, 1996-1998. MMWR 1998;47:151-4.

year were infected internationally, and, because the two AZT regimens were never compared, we still don't know whether the two regimens are equally effective. Interestingly, the CDC investigators in Cote d'Ivoire seem to have little question that the alternative AZT regimen would prove more effective than placebo. In their protocol, the investigators state that "This [AZT] study is proposed in the belief that short-course oral therapy may be as effective or nearly as effective as the [more expensive AZT] regimen."[19] This "belief" should have led to an active-controlled study, not a placebo-controlled trial.

Criticisms of Active-controlled Trials

Before suggesting a solution to this problem, we would like to briefly address two common criticisms of active-controlled trials raised by the FDA and others. The first is that incentives for optimally conducting research are reduced in active-controlled trials, because any sloppiness in conducting the trial will obscure true differences between the therapies being compared. But in an active-controlled equivalency study, the kind we advocated in the AZT studies, the researcher has to prove that the two therapies are approximately the same (the "alternative" and "null" hypotheses are reversed); any sloppiness will lead to a conclusion that the therapies are not equivalent, the opposite of what the researcher is attempting to demonstrate. Second, it is alleged that active-controlled studies do not have established statistical techniques and lead to larger sample sizes than placebo-controlled studies. But appropriate statistical techniques do exist (indeed, the FDA has an entire group of statisticians devoted exclusively to equivalency studies) and the required sample sizes are often quite similar to those needed for placebo-controlled studies. For example, in the AZT studies we calculated that an equivalency study would require 620 subjects, compared to 500 for a placebo-controlled study, not a substantial difference in the world of sample size calculations.

Patients are being ill-served by the rigid adherence to the placebo-controlled dogma. Subjects are being placed at risk needlessly and doctors are denied the information they need to make decisions that are in the best interests of their patients. Furthermore, medications are coming on the market simply on the basis of their being proved better than nothing, regardless of their effectiveness relative to established therapies. As "me-too" drugs continue to flood the market, Americans need to know how these medications compare to one another, not simply if they are superior to placebo, a much weaker standard.

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[19] CDC/Thailand study protocol, January 15, 1996

Legislation to Reduce the Number of Placebo-controlled Trials

Because the FDA so heavily favors placebo-controlled trials, even though existing regulations permit FDA approval based on active-controlled trials, manufacturers, acting in their own self-interest, will continue to sponsor inappropriate studies with placebos. There is little question that most drug companies would rather demonstrate that their drug is better than nothing than take the chance that it may be no better--possibly worse--than the existing treatment. And once a drug is approved using the weaker "better than nothing" standarc, there is little the FDA can do to require companies to conduct comparative studies. So active-controlled studies languish as the poor cousins of the clinical trials family, despite their obvious benefits. Some countries have required pharmaceutical manufacturers to go beyond the mere demonstration of drug safety and efficacy. Norway and Iceland have required data on comparative safety and efficacy. What is needed now is legislative action by the Congress to require active-controlled studies when a known effective therapy exists. In the absence of such action, the FDA will continue its role as one of the major enforcers of the placebo-controlled orthodoxy and subjects, patients, doctors and insurers will continue to pay the price.

Mr. BURTON. Thank you, Doctor. You heard the testimony, Dr. Lurie, of Mr. Foster and his wife a while ago. I guess I gather from our statement that you think a better way to test a new hypertension drug would have been to have Joe take one or the other and have another group take the other kinds of drugs so that there was a comparison as to who did better with certain types of medication, rather than having a placebo?

Dr. LURIE. I think a better way would have been to compare this new experimental drug——

Mr. BURTON. Right.

Dr. LURIE [continuing]. To some drug of known effectiveness, yes.

Mr. BURTON. Right. What do you think about using that new drug with a person who has high blood pressure and have them go on a placebo?

Dr. LURIE. It depends, of course, on the degree of high blood pressure that the patient has. If their blood pressure is minimally elevated and it's not clearly an indication for hypertensive medication, then arguably there might be a place for a very short-term use of placebo. But the longer the period of observation is, the more significant the patient's hypertension is, the more the patient has failed prior anti-hypertensive medication, which seems to be the case for Mr. Foster, the more problematic it becomes.

Mr. BURTON. So with 180/110 blood pressure and a history of high blood pressure, you probably would not have prescribed that he be on a placebo.

Dr. LURIE. If I was the doctor taking care of a patient like Mr. Foster with a blood pressure of 180/110, who, from what we have heard, although obviously I have not seen all the medical records, but who had failed three or four prior medications, as a physician, independent of anything related to a clinical trial, I would not have stopped his medication.

Mr. BURTON. What about a broad test or program where they were investigating this new anti-hypertension drug compared to a placebo where they had large numbers of people getting into that kind of a program?

Dr. LURIE. Well, I'm very cautious about having a situation where things that would be unacceptable in clinical practice somehow become acceptable in research practice. And as some writers on the subject have indicated, permitting clinical practices that are significantly different from accepted research—excuse me, permitting research practices that are significantly worse than clinical ones opens one up to a lawsuit, and indeed, we now see that that's the case. It seems to me arguable that, at a minimum, one would hope that researchers would protect at least as well as clinicians.

Mr. BURTON. It sounds to me in a situation like we were talking about where they were using placebos, as opposed to an experimental drug for people that had hypertension, that there would be a myriad of possibilities of lawsuits for medical malpractice if those people had the problem that Joe had.

Dr. LURIE. You know, I'll leave it up to the medical malpractice lawyers to decide cause and effect, but certainly it is true that they lay themselves open to that.

Mr. BURTON. I guess I don't want to put words in your mouth, but the case that you seemed to be making was where a person's

well-being and health is considered, or should be considered, there shouldn't be placebos; there should be one drug against another, rather than having a drug against a placebo which might endanger the patient.

Dr. LURIE. When there's a known effective therapy, which is certainly the case for hypertension, I mean, we have many drugs on the market for hypertension, and I do not think it is acceptable for patients with the degree of blood pressure that we're told Mr. Foster had, to have his medication, in effect, taken away from him.

Mr. BURTON. Which the FDA, I guess, does at the current time, uses placebos, or allows those placebos to be used in those kinds of medical tasks.

Dr. LURIE. Well, again, I don't think it's a question quite of the FDA—of the FDA doing it. It's a question of what the clinical investigators do and a question of what——

Mr. BURTON. Isn't that—but that's approved, I think, by the FDA and I'll ask Dr. Friedman when he gets up here in a minute.

Dr. LURIE. I think so.

Mr. BURTON. Let me ask you this, Dr. Shamoo, does fenfluramine have any medical benefit to children in single doses to your knowledge?

Mr. SHAMOO. Well, this is the thing which was lost in the first half of the hearing is that——

Mr. BURTON. Can you pull that up closer [speaking about the microphone]?

Mr. SHAMOO [continuing]. That fenfluramine or PCP, or Special K, Angel Dust, or animal tranquilizer or PCP or cocaine, or street drug amphetamine, these are injected in patients. There is no therapeutic or medical cause to do that. They only do that using those patients as guinea pigs, to find out their brain activities—whether serotonin goes up or down, et cetera, that's the only purpose. These children, these youngsters in New York, they were not obese; they were not using fenfluramine for obesity. Their only crime is that they had siblings incarcerated. The court record was broken; they were found out, and then they were given fenfluramine. Their local doctor would have never prescribed or told them "enter into a research protocol to use fenfluramine."

Mr. BURTON. Yes. Let me go one step further. I think I heard the FDA say there was no evidence that fenfluramine was dangerous to children in single or double doses. What's your response to that?

Mr. SHAMOO. Well, I know I have read there are adverse reports on fenfluramine for adults, and quite a number of them, in the hundreds. And there are even 70 deaths reported from fenfluramine. So I don't know——

Mr. BURTON. Is that in single or double doses?

Mr. SHAMOO. No, this is in regular doses. But there are even adverse reactions reported on single doses on adults.

Mr. BURTON. Very well. Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman. Maybe I'm—it's just—I'm just trying to be practical here. If you—I, personally think it's unethical to have a person in a situation where you're giving them nothing, basically, a placebo, and they're suffering. I don't agree on a whole lot with my chairman, but I tell you, this one, I kind of agree. And then you don't—and that person is

not getting anything. And if somebody had done that to me in this experiment, I'd be dead at 180/130. And I'm just trying to figure out, first of all, exactly where—I see the people from the FDA; they're jumping up—I mean, I'm sure you can feel their vibrations at times to some of these questions.

Dr. LURIE. It's getting kind of warm back here. [Laughter.]

Mr. CUMMINGS. But I'm just trying to figure out—so, is this almost a case of we do it because we've been doing it, the placebo thing? I mean, as opposed to the piece where you do—if you got something that works, say like in high blood pressure medication, and you're doing the—you said the comparative thing, you keep the person on the medication, but I still trying to figure out why we would do that, especially with an insensitivity, with an insensitivity, and I say why "we" would do it—I still haven't figured out who you blame for this, but with an insensitivity to the individual. Am I missing something?

Dr. LURIE. Well, let me answer your question in a number of ways. I think Dr. Friedman's testimony was actually quite eloquent on this. In the bad old days of clinical medicine, many medications came on the market without adequate proof of efficacy and that was true until about 1962. It doesn't mean that everything prior to 1962 was ineffective, but good proof really began—of effectiveness—began in 1962.

Part of the way those medications were proven effective was by comparing them to placebo. In some of those studies—and I'm sure the FDA has a large number of these tucked away in their back pockets—patients were better off being assigned to placebo because the drugs were ineffective, and, in some cases, dangerous. So the question to which I'm addressing myself is not to the question of placebo, ever; it's to the question of placebo when we know that something works. OK. Does that——

Mr. CUMMINGS. Yes, I'm more——

Dr. LURIE. We're in the same place there.

Mr. CUMMINGS. OK. Yes.

Dr. LURIE. OK. I'm sorry.

Mr. CUMMINGS. So let's stop right there. And I need a distinction between when a placebo is appropriate and when, in your opinion, it's not.

Dr. LURIE. OK. The——

Mr. CUMMINGS. You see, because I'm thinking—I'm trying to figure out when it's ever appropriate, unless it's the example that you just cited; that is, that the medication that they're on is so bad for them, that maybe they'd be better off not taking it. That's the only—and then the question becomes, how do you know that?

Dr. LURIE. OK. The issue is whether or not a medication is known to be effective, has been proven to be effective. And one way in which you might prove a medication for a particular condition to be effective would be with a placebo-controlled trial, right? You might do it that way once, maybe twice, if the first one was not completely clear. OK?

But at a certain point, medical evidence starts to accrue and there becomes really very little question about the effectiveness of a particular medication, and the examples that I picked, I think, are good ones. The treatment of hypertension certainly is some-

thing that, in general, we like to treat as physicians. Methadone is a well-proven, effective treatment for people with opiate addiction, and the drug AZT dramatically reduced the transmission of HIV from mother to infant.

I don't think there's really any significant quibble over the effectiveness of those medications. In those circumstances, in general, I believe that it would be unacceptable to randomize people to medication—placebo—that we know will not work. That's my point.

Mr. CUMMINGS. OK. All right. Now, it's interesting that, you know, it was recently alleged that Eli Lilly conducts trials with homeless people. I have a lot of homeless people in my district. I have a very poor district. And I'm concerned about the level of consent involved here. It said he provides food, shelter, a stipend to a homeless person. Dr. Lurie, do you feel that the use of homeless participants carries a potential for exploitation? Is there an ethical issue here?

Dr. LURIE. Well, certainly, the more disenfranchised the group of subjects is, the more one has to be careful in protecting them. The examples that I gave, I think some of them, not coincidentally, involved what might be considered disenfranchised groups—drug users, people HIV-positive, poor women in Africa, homeless people, patients with psychiatric conditions. Certainly, I think everybody would agree that those are places where we need to be particularly careful and informed consent needs to be particularly carefully honored in those circumstances.

Let me make the point with regard to informed consent, though, that, unfortunately, the informed consent form has become just that—a form. Indeed, in some cases, a formality. And part of the problem is that even though many studies have shown that in fact subjects are very often not informed, and in some cases are not really consenting in a meaningful way, that the informed consent form becomes in some ways a substitute for real informed consent.

Now, it is very difficult to get good informed consent—unquestionably. But the researchers as a general matter do not make it their practice to go back and prove that people have, in fact, been adequately informed and are adequately consenting. And I think until such time as we have a structure in place that really tries to confirm that, I think that some of these kinds of violations will continue. No one would dream of measuring the patient's blood count without confirming that that machine is really reading correctly. And I think, when we start talking about informed consent, there should be better corroboration that true informing and true consenting is really happening.

Mr. CUMMINGS. Thank you.

Mr. BURTON. Let me just ask you a couple more questions, then if you have any more, Mr. Cummings, with the panel, then we'll conclude and get back to Dr. Friedman.

The fenfluramine kind of bothers me a little bit, Dr. Shamoo. These children that were in this test, as I understand it, were children who had siblings that were incarcerated, that had broken the law, and they wanted to inject this chemical into their brain to find out if it would alter their—alter them so they might not, I presume, commit the same kind of—or have the same kind——

Mr. SHAMOO. Well——

Mr. BURTON. But let me just finish my question. And so a lot of those children, I would presume—and maybe you know more about this than I do—may have come from innercity broken homes where there was a problem already; they had one child that had broken the law, been incarcerated, and the parent may have been in a financially difficult situation. Now, these people, it's been reported to me, were getting $125 per injection for their children, which might have been an inducement for them to sign this informed consent. Can you elaborate on that just a bit? Because you've compared this twice now to the Tuskegee case and you think they were using these kids as guinea pigs.

Mr. SHAMOO. Well, I think it's worse than Tuskegee, and I would like Congressman Cummings really to hear me out. The issue of the placebo, this is worse. This is taking youngsters and adults who are very vulnerable and injecting them with chemicals which have no therapeutic basis. You were talking about hypertensive drugs, which you understand very well. But these people do not need any of these drugs. They are testing what they call "when they are going to fall off the cliff." They're going to keep injecting them with these chemicals until they fall off the cliff.

Going back to fenfluramine, these youngsters have committed no crime. The only crime that's there are their siblings. The paper itself, published paper, said they are in a poor, uneducated environment. What they were testing, Congressman Cummings, whether these children are predisposed, genetically and environmentally, to violence. In our society, we should not even ask such questions in this day and age in 1998, in our great country. That's what they were testing, and their research paper says that.

Mr. BURTON. But the research paper says that they were testing because they wanted to see if there was genetic problem?

Mr. SHAMOO. It's correct, if they were predisposed environmentally or genetically to violence. That's correct, sir. And that is, they want to inject fenfluramine; they see an increase in serotonin. Serotonin is only one chemical, one neurotransmitter. Our behavior is controlled not by one gene or one neuro-transmitter, but literally hundreds and hundreds. To reduce it to one neuro-transmitter is a flawed design; it's a terrible design, and it's an appalling question to ask in our Nation.

Mr. BURTON. I think that's all the questions I have. Mr. Cummings, do you have any more questions of this panel?

Mr. CUMMINGS. Thank you, Mr. Chairman.

Are there a lot of tests like this?

Mr. SHAMOO. Yes, there are five studies on fenfluramine; there are dozens and dozens of tests on other chemicals injecting patients who do not need those chemicals; they are not therapeutic. Like I said, Special K, animal tranquilizers, PCP, amphetamines, street drug amphetamine—these are injected in patients to see when they fall off the cliff, when they become psychotic and delusional. That's the only reason they're using them really as guinea pigs. And these are published as I speak to you.

Mr. CUMMINGS. And, for the last time, where does FDA come into that?

Mr. SHAMOO. Well, some of these—some of these, if they are drugs, approved drugs, FDA comes in the fact that they give them

a fig leaf; they claim this is an FDA-approved drug, and therefore, they can do the experiment. But there is in this country a huge amount of pre-clinical trials supported by the National Institute on Mental Health, all across the country, tens of millions of dollars of such kind of experiments. And they know about it; we have written to them repeatedly; we have told them repeatedly. And they say just "Thank you very much. We're doing just fine."

Mr. CUMMINGS. So, when they say this is an FDA-approved——

Mr. SHAMOO. Drug.

Mr. CUMMINGS [continuing]. Drug, I guess I'm trying to figure out—when they are, if they are experimenting with something, it's not FDA-approved. It's trying to get approval. Is that right? No?

Mr. SHAMOO. No, usually these drugs—and these ladies and gentlemen behind me would know this better—once a drug is approved for certain indications, for certain illnesses, it can be used experimentally for other illnesses.

Mr. CUMMINGS. Right. OK. And this is one that was kicked off the market in 1997. Why was it——

Mr. SHAMOO. And continued to be used afterward.

Mr. CUMMINGS. Why was it thrown out?

Mr. SHAMOO. Why the FDA pulled it out?

Mr. CUMMINGS. Yes, in 1997, yes.

Mr. SHAMOO. I presume they heard a lot of adverse reports on this drug and, again, they could answer it better than I can.

Mr. CUMMINGS. OK. But I've got to ask you—I mean, I want to—because you're probably not going to come back up here, so I just wanted to get this. I take it that's unusual for a drug to be disqualified and then used after it's disqualified?

Mr. SHAMOO. No, it's not unusual. The FDA, I think they will tell you, I think he testified in the first part that that is done routinely. Again, he could talk for himself.

Mr. CUMMINGS. Did you have something to add?

Dr. LURIE. I just wanted to make just one observation with regard to Institutional Review Board review, which is, by the sounds of the presentations that I heard from the previous panel, it seems to point out an additional problem in the oversight of the ethical conduct of clinical research, which is the growing phenomenon of industry-funded research which occurs outside of the realm of universities. When the research occurs in universities, we have well-established Institutional Review Boards that, whereas they certainly have their flaws, act as some kind of protection.

But what we have increasingly with the move toward industry-funded research is what might be called "for-profit Institutional Review Boards" that have sprung up and that serve as the so-called ethical review for these studies. And I believe, if I heard correctly, that that was the case for both of the two studies that were mentioned by the previous panel. Very obviously, a for-profit Institutional Review Board has a conflict of interest, because were they to be seen as an Institutional Review Board that consistently turns down studies for being unethical, the market would operate and less stringent Institutional Review Boards would be favored.

So I think that that is a whole area of protection of human subjects that has to date eluded adequate regulatory scrutiny.

Mr. CUMMINGS. Let me ask you this: Well, with the changes in the health care industry taking place, do you see that—and I notice it everywhere, hospitals are merging; you've got managed care. I'm just trying to figure, how does that, if at all, play into more and more non-university-type research happening?

Dr. LURIE. Well, again, without being able to quote you hard numbers on this, my impression is that increasingly research is occurring outside of the university setting and the for-profit IRB was something that was very little heard of some years ago. But we hear more and more of it now. So I, again, I urge you to look at that as something that, you know, you might look at more closely.

Mr. CUMMINGS. Thank you.

Mr. SHAMOO. May I add something to this, Mr. Chairman?

Mr. BURTON. Yes.

Mr. SHAMOO. About the IRBs. I'm not as sanguine as he is about university IRBs. There are over 4,000 IRBs decentralized all across the country. Usually, they're composed of 20 faculty members, my peers and colleagues I eat dinner with; they review my grants; I review their grants, and they have one from the community. That is really not a good gatekeeper. What should be, the majority should be from the community where the patients are coming from and then the minority from the institution.

So, a lot of these problems you may not know about. The bulk I deal with, they are from IRBs in universities.

Mr. CUMMINGS. I just have one more question, Mr. Chairman. I mean, just what you just said, I guess, if I'm sitting there and you're my buddy, we're playing golf together, and we're both at the university, and if I vote against your thing, that has a direct financial effect on you, am I right?

Mr. SHAMOO. Exactly.

Mr. CUMMINGS. OK, that's all.

Mr. BURTON. If we could have your recommendations on this subject, we certainly would like to have it—not that we can do anything about regulations, but we can at least talk to the FDA about it.

Thank you very much. We appreciate your comments.

Dr. Friedman? If we could have you come back up for just a few more questions. Obviously, we're down near the end of the road here, so we'll let you and your colleagues—I wouldn't mind asking Dr. Temple a question or two, if he wouldn't mind coming up as well.

Dr. FRIEDMAN. That would be fine, sir. And if I could take the opportunity—there are just a couple thoughts that if I may share with the committee, I would be very grateful for that opportunity.

Mr. BURTON. Sure. Well, let me ask you a couple of questions first.

Dr. FRIEDMAN. Please, yes, sir.

Mr. BURTON. What percent of the tests that FDA approves include a placebo as opposed to another drug of comparable quality? In other words, do most of your tests that you approve of have a placebo?

Dr. FRIEDMAN. I think the statement that was made by Dr. Lurie just a moment ago is very important in this regard. He correctly recognized that there are whole portions of FDA, whole divisions,

that barely use placebo-controlled trials ever. Infectious disease and oncology, cancer therapy, are the two that he named, and he's absolutely correct in that regard.

There are other parts of the agency and other kinds of diseases where these are more commonly used. So that, I think—I don't have a numeric answer to your question. I'm sorry, sir, we can attempt to do that, but there are portions of the agency where we completely agree with Dr. Lurie and others that there is no place for placebo trials, and others where we think it's scientifically much harder to determine.

Mr. BURTON. What we'd like to have is, if you could give us some kind of a breakdown on how you determine whether or not you do it one way or the other, if you could send that to us?

Dr. FRIEDMAN. I would be happy to, sir.

In that regard, though, I must make this comment: The issues that are being raised with respect to placebo trials are very important, but I think that you're going to have only a fraction of the answer and you're going to have not complete, not the kind of insight that you want to the problem, unless you have at the table NIH, the pharmaceutical industry, investigators, people who can speak cogently. We spent a lot of time discussing hypertensive trials.

Mr. BURTON. Right.

Dr. FRIEDMAN. And that's a very complicated area. But properly, that is discussed by—this is not FDA saying to the world that you must do it this way; you've heard some very thoughtful, careful thinking people describe their concerns. I respect that. But I think, to have the fullest discussion, you need to have the people from NIH, from OPRR, from the local investigators, about what concerns or what are the other issues they're raising. These are very important issues and they're very complex issues.

Mr. BURTON. Let me just say that obviously I think you know and probably it's a problem for men of medical learning such as you folks to come up here and talk to laymen, but we do have oversight responsibilities—no, I'm not criticizing.

Dr. FRIEDMAN. Yes, I'm happy to do it, sir.

Mr. BURTON. And so what we need to do—what we need to do is get the various parts of the picture, so that we can understand it.

Dr. FRIEDMAN. Yes.

Mr. BURTON. And we will be talking to NIH and the other people that you talked about to get additional—and some people from the pharmaceutical industry.

Let me ask you this: How many people in experimental programs are not reported that are dropped out or washed out? I think one of the doctors that preceded you indicated that 88 percent did not report any dropouts to the pharmaceutical companies when they did these tests.

Dr. TEMPLE. I can't imagine where that information comes from. In the various classes of drugs Dr. Shamoo was talking about, the dropout rates from many studies is in the neighborhood of 50 percent, and it's always reported. We also know that there are suicides that occur in both the treated and untreated groups. In the studies of anti-depressants, there's a published study by Eli Lilly of their

experience with Prozac, involving over 3,000 people, in which they made the case that the number of suicides was the same in both groups. We're aware of suicides in those trials. I don't know where he gets that.

Mr. BURTON. Well, this Mr. Foster that we had before us—I guess there's no way of determining whether or not he was included in the statistics you're talking about?

Dr. TEMPLE. We can find out.

Dr. FRIEDMAN. If I may, let me speak to that, if I may.

Mr. BURTON. How can you find out?

Dr. FRIEDMAN. Well, we can't, sir. And let me tell you——

Mr. BURTON. You can't?

Dr. FRIEDMAN. We cannot.

Mr. BURTON. Because it's coded?

Dr. FRIEDMAN. We do not have patient-specific information.

Mr. BURTON. OK, but this is important. This is important. Because it's coded. So you don't know when there's a washout because the pharmaceutical company keeps those records. You don't know what the person's name is who washed out or the ones that stayed in the program?

Dr. FRIEDMAN. That, in terms of——

Mr. BURTON. So how do you know——

Dr. FRIEDMAN [continuing]. Confidentiality, that is absolutely correct, sir.

Mr. BURTON. So how do you know, then, that the records that they give you are accurate?

Dr. FRIEDMAN. That's a very important question. The quality of the records—I was going to say—we do onsite inspections where we look to see whether patient information that is recorded in the local records is consistent with the records that are submitted to the pharmaceutical companies, the sponsor, and ultimately, to the Food and Drug Administration. I personally have participated when I was an investigator, and when I was at the National Cancer Institute, I personally participated in both sides of those record inspections, sometimes conducted by the Food and Drug Administration, sometimes conducted by the National Institutes of Health.

Mr. BURTON. I understand, but how do you check when all you get are code numbers rather than people's names? I mean, is there some kind of a double-check so that the code numbers are in sequential numbers, or sequential order, so that they can't drop somebody out without you knowing it?

Dr. FRIEDMAN. There certainly—when a patient is assigned, depending on the specific clinical trial, when a patient is assigned, that individual has a number, and once that number is assigned, there is followup for that individual.

Mr. BURTON. Joe said there was no followup on his case.

Dr. FRIEDMAN. Well, that's a very important point, sir. Can I just talk about that for a second?

Mr. BURTON. Sure.

Dr. FRIEDMAN. Because that's really important. Obviously, I don't know the specifics of the case here—of either of the two grieving families that we heard from today. The kinds of criticisms that were talked about and the concerns that were raised are very serious concerns. But it's not at all clear to me whether those concerns

relate to the Food and Drug Administration, whether they relate to the OPRR and the local IRB operations, whether there are State or local medical society issues having to do with the practice of medicine. I think these are profoundly important questions and these are troubling cases, but I don't know the details of the specific cases, and I say this with the greatest respect and not meaning to sound critical at all. I do not intend to be critical, sir. There were important misunderstandings, one might even say mistakes, that were made, by the individuals testifying, not out of malice, but out of misinformation that they were given.

The most prominent example was the mistaken notion that FDA gives money or funds grants for the study of psychiatric products. The National Institutes of Health do; pharmaceutical companies do; local institutions do; universities do. We fund very few, if any, grants and we don't fund the kinds of grants that were being talked about here.

So there are a lot of serious issues, but I'm sorry to say it's too bad that the way in which the information is presented and the way that this committee is analyzing this information tends to obscure and make it more difficult to come to conclusions.

Mr. BURTON. If Mr. Cummings would just let me have a few more questions here?

Dr. FRIEDMAN. Please. Yes, sir.

Mr. BURTON. So if someone like Joe Foster wanted to find out if he'd been reported to FDA in the numbers report or the coded report, how would he do that?

Dr. FRIEDMAN. We do not have by name specific information that we can then identify and say "this record relates to this particular individual."

Mr. BURTON. OK, so let me ask you this: So you want to find out about Joe Foster's problem. How do you do it?

Dr. FRIEDMAN. If we——

Mr. BURTON. You're the head of the FDA. How do you do it? You know the pharmaceutical company that was working on the case. How would you do that?

Dr. FRIEDMAN. Well, I think the question is whether it was part of a concern that we had about the quality of the data, in which case——

Mr. BURTON. It's a concern now. How would you do it? How would you find out about all the circumstances surrounding Joe's case?

Dr. FRIEDMAN. As I was about to say, sir, I think it depends upon the circumstances. If we believe that there is an investigation going on that has to do with the quality of the data, the sort of questions that you were raising, then we would have one of our inspection teams review the information either at the local site where the research was conducted, or work with the pharmaceutical industry.

Mr. BURTON. So the pharmaceutical company would give you that information?

Dr. FRIEDMAN. No, not necessarily. I think that we don't——

Mr. BURTON. Then how do you find it out?

Dr. FRIEDMAN. I was going to say, when the inspector is onsite, those records would be available for inspection and they do have the patient-identifying numbers or codes or the patient's name,

when there's an inspection at the plant or at the facility or at the research site. Maybe Dr. Temple would like to——

Dr. TEMPLE. Well, one of the things we worry about all the time is whether something important is not being reported to us. You've been focusing here on whether someone in a washout period didn't have something reported. We also worry about whether an adverse reaction to a drug wasn't reported. So we could—and if we heard, or there was suspicion, that something was not reported, we can go to that site, find the available records, and see whether it was reported. There ought to be a—if Mr. Foster was in a trial, there needs to be a record of that. These records have to be maintained and we can go read it. So, does that mean that the record couldn't have been made to disappear? Well, no, but——

Mr. BURTON. Well, let me just say that if there's a way you can do that, he's a person who has $220,000 in medical bills, was a washout, was given a placebo which led to a stroke and a heart attack. I would like to know, and I guess we could have a consent form signed by Mr. Foster—I can get a consent form that legally would allow me as a Congressman to get that information. I would like to know how you'd check that out. Because I—from what you told me today, it sounds like to me that the FDA has a very limited ability to check into these washouts, these people that may have been given placebos that had problems, and it may have distorted, the information that you're getting, from which you're making determinations. I'd just like to know and we have one specific case, Joe Foster. I'd like to know about Mr. Foster.

And with that, I yield to Mr. Cummings.

Mr. CUMMINGS. I just want to followup on what the chairman was just saying. I guess it's one thing to have the ability to get this information, and I guess it's another thing to—I just guess you've got a lot of considerations here. The more I listen to this, the more complicated I see that it is.

Dr. FRIEDMAN. Yes, sir.

Mr. CUMMINGS. Yes. First of all, tell me—help me with the Institutional Review Boards. What part do they play? Apparently, they play some part.

Dr. FRIEDMAN. Yes, sir.

Mr. CUMMINGS. And do you ever—you may, you said a few statements about Institutional Review Boards and the problems with them. Do you all have any—is there an occasion that would cause you to look at an Institutional Review Board with regard to the kind of issues we're talking about today?

Dr. FRIEDMAN. There certainly are cases—we certainly do have site visit activity when we visit Institutional Review Boards to look at the adequacy of their recordkeeping, whether they meet with—they have the right—the point that you made earlier about the constitution of the committee. Is there a representative from the community? Is there representative of this or that discipline? We look at those sorts of things.

Mr. CUMMINGS. Now, while you're on that, who controls that? Does the State law control that? Does Federal law control that? Is there FDA regulation as to the kinds of composition on those boards?

Dr. FRIEDMAN. It's a shared responsibility between the Office of Protection of Research Risk, OPRR, for NIH or federally sponsored research and the kinds of universities that the doctors were talking about previously are largely, although not exclusively, governed by that. But there are also our FDA regulations that have to do with the quality of that committee and their constitution and how they meet.

So it's a shared responsibility, and you're quite right to say it's complicated. And that's why I kept harking back to the point that, unless we have everybody at the table who has a role to play, you only get a sort of fractional view of it.

Mr. CUMMINGS. Now, do you have enough money to do your investigations and things like that? I mean, we're here talking about the ability. It takes money to do a lot of these things. Do you all have enough money? We are the Congress of the United States of America, and I'm just wondering—and we do have appropriation powers—I'm just wondering, do you have enough money to do what you're supposed to do? In other words, I don't want you to——

Dr. FRIEDMAN. I'll give you a longer answer than you would like, but I'm happy to try and respond. We certainly participate in the administration's budget-planning process and we are thoroughly committed to the Balanced Budget Amendment. We have at any moment in time, like many other agencies do, a larger list of what we think are important ways to serve the public than we can complete at any moment in time.

We recognize that there are many parts of Government that say that. I would say to you, sir, that we are trying to optimize how we conduct this activity. We are at the moment very stretched, trying to match all of the mandates that we have and all of the responsibilities, the ways we want to serve the public, with the resources that are available. And I don't say that with any complaint, but to say that is a tremendous challenge for us, and we think that we're going to have to continue to struggle with that for the foreseeable future.

Mr. CUMMINGS. Now finally, with regard to these Institutional Review Boards, that is—and then hooking them up with the drug trials—what part do they play with regard to the criteria, whether or not there's going to be a placebo——

Dr. FRIEDMAN. Right. Very good.

Mr. CUMMINGS. Do they have some say with regard to that?

Dr. FRIEDMAN. Absolutely. In order for clinical research to be conducted at an institution, you have to have that clinical protocol reviewed by the institution. That institution, that review board, looks at the protocol which describes the research experiment, looks at the consent form, looks at the investigator to see whether that person has a good reputation locally for having quality work done. And that research cannot go forward without the specific endorsement of the IRB.

Now, at yearly intervals, you're supposed to report back to the IRB an update of what's happened over the past year and plans for the future. You also should report to that IRB any unusual toxicities, unexpected deaths, things like that. That's the way, when I served on an IRB, that's what I expected, and when I reported to an IRB, that's what I did.

Now, granted, it was a really fine university IRB, and I just think the world of the people who were my colleagues on it, but they would take no—they had very little tolerance for anything but quality. They were not buddy-buddy. They were scrupulous. They were even ruthless about looking out for patient interest. That's my experience and I think that it's not so uncommon at other IRBs as well.

Mr. CUMMINGS. I just have two questions, Mr. Chairman. You're right, we need to be right now. So you've got the IRB and if they're doing—I'm sorry, you don't have your name tag up there——

Dr. FRIEDMAN. Dr. Temple or Dr. Nightingale.

Mr. CUMMINGS. And they're doing what Dr. Temple talked about a few minutes ago; you're my golf partner; I'm your golf partner; we're buddies; we're on the review board, we've got some research going on, whatever, and we're trying to, you know, help out each other, and they do some things that are unethical, or there are some real questionable things that could lead to some of the disasters that we've heard about today. Where does the FDA come into that process? See, I'm trying figure out who's to blame for all of this.

Dr. FRIEDMAN. Let me answer it two ways, and I don't mean to be pointing figures and say, "Oh, it's not our responsibility." That's not my intention here at all. The issues that we heard today legitimately may have to do with the quality of practice by the practitioner who was involved. I don't know. I'm not making that judgment. But I'm saying that that's a real question that several people asked. The term "malpractice" was brought up; the oversight of the local facilities by State and local medical societies who have licensing and other authority; OPRR for looking at the quality of the research that's being conducted; NIH if some of that research was supported by the National Institutes of Health, and my understanding is that at least for some of the things we're talking about it was NIH-supported.

And in addition to that, we have a responsibility for seeing that the IRB is properly constituted, that the informed consent documents are appropriate and are signed and are kept on record. Now, I absolutely agree with Dr. Lurie who said that it is very hard to get informed consent and a document is only the beginning of that process. But it is an essential part of that process.

Mr. CUMMINGS. Let me ask you this: I think this is my final question. This New York case—do you have a—I mean, from what you know about it, do you have a problem with it? Because I do.

Dr. FRIEDMAN. Sir, I must tell you that I don't know enough about the case. I can assure you that I'm going to be looking into it much more carefully. I can assure you that I'm not making any assertions about the quality of this or that. We're going to look at everything.

But it may be possible—and I just want to say this clearly—it may be entirely possible that the questions that are being raised here have really good answers, that if we had known about this, we would have had those answers ready and we could have dealt with this. And I just have to say that, even if we weren't responsible, tasked with having that responsibility, if this is an NIH study, they should be sitting here. If there are investigators, they

should be sitting here. If there are other people involved in it, they should be sitting here. I should be sitting here, too. I'm not shirking that responsibility, but it is difficult to try and answer questions about something where I don't have complete information.

Mr. BURTON. We have about three or four votes coming up. I have just a couple more questions. Are you about finished?

Mr. CUMMINGS. I just wanted to say, Mr. Chairman, that I—you know, this has been very interesting and I think that if we really want to get to the bottom of this, we really do need to bring in more players and try to——

Mr. BURTON. Well, we will do that.

Dr. FRIEDMAN. Mr. Cummings, let me assure you, sir, I will look into this. I don't mean to imply anything else.

Mr. CUMMINGS. Believe me, you were fine. Thank you.

Mr. BURTON. Let me just say this: I have one more question of Dr. Temple. Before I ask him this last question, the concern that I have is the average person like the victimized people we had here today and the ones we've had before, they don't know that you have to go to four or five agencies to find out where the responsibility lies. Now, you've told us here today that we need to get NIH in here, and you, and other agencies in here because they're shared responsibilities. You do this part; they do that—that is just, that is just unbelievable. The people out there in the hinterlands, they have to deal with these problems and they don't know where to go. They think it's FDA. I thought it was FDA. Now you're telling me there's other agencies involved which we will talk to. But it seems to me there has to be some ultimate source of responsibility, so that we know where to go to find the answers.

Even this stuff we're talking about with the coded names of people in the pharmaceutical industry, and I'm going to give you a formal letter asking—and get a consent form signed by Mr. Foster, so that we can have you go and investigate that because there is a lot of money involved.

But it seems to me that there's something that has to be done by the Congress probably to have some ultimate source of responsibility for all this because you can't have this kind of fragmentation and have the American people feel like there's any confidence in government, especially when they have health problems.

I have one last question. And you might think about that and maybe talk to your compatriots in the other agencies about some kind of way to deal with that.

Dr. Temple, you state that a placebo-controlled trial could not be conducted in a case where a life-threatening disease is being treated, and there's an established treatment known to prolong life. However, you then go on to describe how placebo-controlled trials can be effectively carried out even with conditions such as hypertension, unstable angina, and even epilepsy, for people being treated. You wrote about a trial done on a drug for acute angina where subjects were taken off the drug for only a 1- to 3-day period. Even in that controlled setting, you reported that six of the patients did not complete all 3 days of the study. You said, and I quote, "they left for administrative reasons, death, or acute infarction." Some would argue that placing trial subjects at risk for acute infarction is unethical, given the irreversible nature of those outcomes.

Now, how can the FDA maintain that that kind of testing is ethical?

Dr. TEMPLE. Let's do the last first. That was not a trial where there was existing therapy. That was the first trial in unstable angina of a drug called Verpamil, and the number of people, those six people, came from both treatment groups. So I think that's been somewhat misinterpreted. That is, that was used to illustrate another point about how to do a trial.

Dr. FRIEDMAN. You look confused, Mr. Burton. May we clarify that?

Mr. BURTON. I am confused. I mean, you know——

Dr. FRIEDMAN. That was the first trial—what Dr. Temple has just said, that's an old trial. It was the first trial of a treatment for unstable angina. It was exactly the situation that Dr. Lurie said would be appropriate for a placebo-controlled trial where there wasn't an established treatment.

Mr. BURTON. So this was prior to established treatment, you're saying?

Dr. FRIEDMAN. And, and that the deaths that have been described are both from the treated group and the placebo group. That's what I heard Dr. Temple just say.

Dr. TEMPLE. That's right. I don't remember the numbers of each, but I know they were present in both groups. That was part of a paper designed to illustrate a trial that we thought was a reasonable way to go ahead in a condition that was frightening to people. People were on placebo actually for only 1 day. And then, depending on their response, they were moved to therapy. But there was no known treatment that was effective at the time.

Mr. BURTON. Would you say, then, that you don't agree with further placebos in this kind of a trial?

Dr. TEMPLE. No. That depends. Can I just—you could believe from the testimony you heard that the reason we like placebo is whim or stupidity. But that's not the reason. The problem with the alternative kind of study that people have talked about, Dr. Lurie in particular, the equivalence trials, is that there are many circumstances in which it's not informative. The failure to show a difference between two treatments doesn't necessarily mean that either of them work.

Now, that's a long and complicated matter. I have lots of examples in things that I've published, but for the moment, take my word for it. To the extent that's true—to the extent that's true, a showing of equivalence is not good evidence that a drug works. If an anti-depressant isn't shown to work, marketing it to millions of people is not a favor to them.

Mr. BURTON. Well, let me interrupt. I've got to go vote. How much time's on the clock? I have to live by a clock, like all of us do.

Dr. FRIEDMAN. Yes, sir.

Mr. BURTON. But you take a person who has hypertension and you put them into a program where there is a placebo, and they have the kind of outcome that we've seen here today. That is, it seems almost criminal.

Dr. TEMPLE. Well, the kinds of trials that we——

Mr. BURTON. And how do you check the IRB in question to make sure that they're doing this properly?

Dr. TEMPLE. The kinds of trials that we would allow in hypertension would be trial in people with mild to moderate hypertension, not severely ill. They would certainly have to be closely monitored and the trials would be very short.

Mr. BURTON. Well, this fellow today, Joe, 180/110——

Dr. FRIEDMAN. Sir, again, we don't have all the information, but let me just say, what he said was he wasn't even eligible for the trial, is what his physician told him. That's my understanding. So that if that—it sounds like he was not—again, I don't have the information, but just listening to this very poignant testimony, it sounds like he was not a candidate and should not have been entered on the study. That's what they said. OK, but I mean, that's what we're led to believe or that's the information that we have.

So his situation, again, are there circumstances in which under very carefully controlled situations you can go to a patient and say "would you permit yourself, would you agree to participate in this trial?" The critical issues here are full informed consent, and we've heard that there's considerable question about whether this patient understood what was being offered or if that information was provided; I'm making no judgment, but from what I've heard today, that patient did not have all the informed consent that he and his wife would have wanted to make that decision. And then it's a matter of choice for the physician and for the patient.

I have had patients who have told me they have such intolerance of their current treatment, even though it is a reasonable treatment, even though it has benefits for them, that they would rather stop that treatment and try something new rather than continue with the side effects of that treatment. I'm not judging whether that's right or wrong. I think our responsibility is to make sure that the information is there, that it's conveyed properly to the patient, and that the patient and his family get to make an informed choice. Those things may not have occurred in this situation. They may not have occurred. I clearly hear what they're saying. But that's not a design in the study problem. That's that this may not have been the right patient; this may not have been the right circumstances.

Mr. BURTON. Well, I guess you know I have people in my family that have hypertension and I think everybody does. And how closely would you have to monitor somebody to be able to prevent or guarantee that they're not going to have a stroke?

Dr. FRIEDMAN. Well, again, I think that that's a very important question and the relevant people——

Mr. BURTON. And that's why I don't understand—I don't understand placebos.

Dr. FRIEDMAN. Let me explain to you, sir, that there are plenty of people who walk around with very mild hypertension, and for those people you say to them, as a physician, I say to those people, "Would you please try and lose 10 pounds? Would you go on a low salt diet? Would you try and quit smoking? Would you try and exercise?" Those people are untreated, while I say to them: Know that all drugs have side-effects. We know these lifestyle changes

can have important ramifications. "Would you please try that and then you won't have the side effects of the medicine? "

I'm not saying that's untreated, but it isn't drug therapy, sir. And again, without having the Heart, Lung and Blood Institute, without having people from the American Cardiology Association, other people who can speak really in an informed manner about this—this is a really complicated issue that you deserve to have all the information on. It's a common problem in the United States. Mr. Cummings made the very, very important point that, especially in the African American community, this is a terrible killer.

But to have a full discussion of when you use placebos, how you use washout periods in hypertension, is beyond the scope of the few minutes that we have left. It deserves a fuller discussion.

Mr. BURTON. Well, we will send you a list of questions and we'll contact some other people.

Dr. FRIEDMAN. Thank you, sir.

Mr. BURTON. And we'd also like to have the answers to the questions that we have asked regarding the informed consent.

Dr. FRIEDMAN. We look forward to getting all those questions and we'll respond.

Mr. BURTON. I appreciate very much your cooperation. The meeting stands adjourned.

Dr. FRIEDMAN. Thank you, Mr. Chairman.

[Whereupon, at 4:09 p.m., the committee adjourned subject to the call of the Chair.]

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