

**INSTITUTIONAL REVIEW BOARDS THAT OVERSEE
EXPERIMENTAL HUMAN TESTING FOR PROFIT**

HEARING
BEFORE THE
SUBCOMMITTEE ON OVERSIGHT AND
INVESTIGATIONS
OF THE
COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES
ONE HUNDRED ELEVENTH CONGRESS

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INSTITUTIONAL REVIEW BOARDS THAT OVERSEE EXPERIMENTAL HUMAN TESTING FOR PROFIT

THURSDAY, MARCH 26, 2009

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:03 a.m., in Room 2123 of the Rayburn House Office Building, Hon. Bart Stupak (chairman) presiding.

Members present: Representatives Stupak, Markey, DeGette, Christensen, Green, Waxman (ex officio), Walden, Burgess, Gingrey, Barton (ex officio), and Blunt.

Staff present: Karen Lightfoot, Communications Director, Senior Policy Advisor; David Rapallo, General Counsel; Theodore Chuang, Chief Oversight Counsel; Dave Leviss, Deputy Chief Investigative Counsel; Scott Schloegel, Investigator, Oversight & Investigations; Stacia Cardille, Counsel; Erik Jones, Counsel; Ali Golden, Investigator; Jennifer Owens, Special Assistant; Caren Auchman, Communications Associate; Paul Jung, Public Health Service Detailee; Kenneth Marty, Detailee; Karen Christian, Counsel; Alan Slobodin, Chief Counsel; and Peter Kielty, Legislative Analyst.

OPENING STATEMENT OF HON. BART STUPAK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. STUPAK. This meeting will come to order. Today we have a hearing entitled Institutional Review Boards that Oversee Experimental Human Testing for Profit. The chair and ranking member and chairman emeritus will be recognized for 5 minutes for opening statements. All other members of the subcommittee will be recognized for 3-minute opening statements. I will begin. Experimental medical testing on human beings has a troubling history. From the atrocities perpetrated by the Nazis in World War II to the famous Tuskegee study in the 1970s when subjects were denied treatment for syphilis, we have learned that we need strong controls in place to protect the health and safety of people who participate in medical experiments.

Under current federal law, medical testing of human subjects that is federally funded or relates to federally regulated drugs or medical devices cannot proceed without the approval of an Institutional Review Board, a panel of doctors, scientists, and non-scientists charged with ensuring the health and safety of the people

participating in the study. Our committee began investigating IRBs in 2007. We learned that Copernicus IRB allowed the study of an antibiotic Ketek to continue without examining reports of fraud it had received. As part of our continued investigation, we asked the Government Accountability Office, GAO, to conduct undercover testing of the IRB review process. We wanted to know whether IRBs are rubberstamping research studies, whether clinical researchers are IRB shopping or choosing IRBs based on how quickly and how inexpensively they approve studies, and whether government oversight of IRBs is adequate.

Today we will hear the results of GAO's investigation, and they are not reassuring. GAO will explain how Coast IRB, a for-profit company, approved a fictitious study led by a fictitious doctor and submitted by a fictitious company. It called for a full liter of a fictitious product, in fact, the same amount in this bottle here, to be poured into a woman's abdomen cavity after surgery supposedly to help healing. GAO's fake protocol was based on an actual high risk study for a product that the FDA ultimately withdrew from the market because of deaths and infections among patients. Besides Coast IRB, GAO also sent its fictitious study to two other IRBs that they both rejected our proposal out of hand.

Here are some of the things that two other IRBs said after reviewing the fake GAO study. The experimental design was the most complicated thing that I have ever seen. During a surgery, a major operation on a patient, a mystery guy walks in and dumps the solution in the body. Where is the safety for the patient? It appeared that people were just going to go out and start injecting. We realized it was a terrible risk for the patient. It is the worse thing I have ever seen. But Coast IRB approved the protocol unanimously 7 to nothing.

The doctor with primary responsibility for reviewing the study told other board members that the protocol looks fine, and that the substance to be injected in the abdominal cavity was probably very safe. Nobody at Coast IRB ever reviewed any of the data cited in the proposal to support those claims. If they had, they would have discovered it did not exist. A doctor who reviewed the study did raise a question about if the study's claim was accurate and that the substance had been approved previously by the FDA, but no one ever followed up with the FDA to answer this question, and in an e-mail to the rest of the board members, the doctor stated it would not have made any difference, that he would have approved the study anyway and that the lack of FDA approval won't affect my recommendation.

The board chair told us she relied on this recommendation and voted to approve the study even though she did not read the full protocol. Why was this review so shoddy? The evidence suggests that Coast was more concerned with its financial bottom line than protecting the lives of patients. According to Coast's CEO, who will testify today, Coast had a practice of voting on research protocols within 48 hours of the board receiving them. One of the testimonials that Coast sent to prospective customers reads thank you very much. You guys are the quickest IRB I ever worked with, and I have done this 7 years. Coast even sent a coupon offering to

give free IRB review so researchers could coast through your next study.

After this committee wrote to Coast IRB requesting documents associated with their approval of this fictitious study, Coast officials took pride in that they were able to discover the study was bogus, but this was 5 months after they approved it. Coast CEO, Mr. Dueber, told our staff within seconds they were able to determine that this was not an actual medical device, and within 4 to 5 hours they determined that this was a sham. Had any of the staff done the research before they approved our bogus protocol 5 months ago, Coast IRB would not be testifying today. GAO's investigation also exposed other problems with the IRB system. GAO was able to create a fictitious IRB that it registered with the U.S. Department of Health and Human Services, HHS, with no questions asked.

The president of this fake IRB was this dog, Trooper, who is, sadly, now deceased. Trooper didn't know anything about protecting human testing, but for a three-legged dog he sure could catch a Frisbee. GAO created a fake web site for Trooper's IRB called Maryland House. It received real inquiries from real researchers and actually had one research protocol submitted for review. When asked why it selected GAO's fake IRB and Trooper to conduct its study, a research coordinator stated that it was because of the low price and the quick turnaround time.

GAO's findings raise serious questions, not only about specific IRBs involved in this investigation, but with the entire system for approving experimental testing on human beings. As a society, we have a moral obligation to ensure that human testing is done in the most responsible and ethical manner. I look forward to the testimony today, and I hope we can discuss ways for both government and industry to fulfill its obligation. That concludes my opening statement.

[The prepared statement of Mr. Stupak follows:]

**Energy & Commerce Committee
Oversight & Investigations Subcommittee
“Institutional Review Boards that Oversee
Experimental Human Testing for Profit”
Chairman Bart Stupak
Opening Statement
March 26, 2009**

Experimental medical testing on human beings has a troubling history. From the atrocities perpetrated by the Nazis in World War II to the infamous Tuskegee Study in the 1970s when subjects were denied treatment for syphilis, we have learned that we need strong controls in place to protect the health and safety of people who participate in medical experiments.

Under current federal law, medical testing of human subjects that is federally funded or relates to federally regulated drugs or medical devices cannot proceed without the approval of an “institutional review board” — a panel of doctors, scientists, and non-scientists charged with ensuring the health and safety of the people participating in the study.

Our Committee began investigating IRBs in 2007 when we learned that Copernicus IRB allowed the study of the antibiotic Ketek to continue without examining reports of fraud it had received.

As part of our continued investigation, we asked the Government Accountability Office to conduct undercover testing of the IRB review process. We wanted to know whether IRBs are rubber stamping research studies, whether clinical researchers are “IRB shopping” or choosing IRBs based on how quickly and inexpensively they approve studies, and whether governmental oversight of IRBs is adequate.

Today we will hear the results of GAO’s investigation, and they are not reassuring. GAO will explain how Coast IRB, a for-profit company, approved a fictitious study, led by a fictitious doctor, and submitted by a fictitious company. It called for a full liter of a fictitious product — the same amount as in this bottle — to be poured into a woman’s abdominal cavity after surgery, supposedly to help with healing. GAO’s fake protocol was based on an actual high-risk study for a product that FDA ultimately withdrew from the market because of deaths and infections among patients.

Besides Coast IRB, GAO also sent its fictitious study to two other IRBs, and they both rejected it out of hand. Here are some of the things those two IRBs said after reviewing the fake GAO study:

- “The experimental design was the most complicated thing I’ve seen. Doing a surgery, a major operation on a patient, then a mystery guy walks in and dumps the solution in the body. ... Where is the safety for the patient?”
- “It appeared that people were just going to go out and start injecting.”
- “We realized it was a terrible risk for the patient.”
- “It is the worst thing I have ever seen.”

But Coast IRB approved this protocol unanimously, 7 to 0. The doctor with primary responsibility for reviewing the study told the other Board members that the protocol “looks fine” and that the substance to be injected into the abdominal cavity was “probably very safe.” Nobody at Coast IRB ever reviewed any of the data cited in the proposal to support those claims. If they had, they would have discovered that it didn’t exist.

The doctor who reviewed the study did raise a question about whether the study’s claim was accurate that the substance had been approved previously by the FDA. But nobody ever followed up with the FDA to answer this question. And in an e-mail to the rest of the Board members, the doctor stated that it would not have made any difference, that he would have voted to approve the study anyway, and that the lack of FDA approval “won’t affect my recommendation.” The Board chair told us she relied on this recommendation and voted to approve the study without even reading the full protocol.

Why was this review so shoddy? The evidence suggests that Coast was more concerned with its financial bottom-line than protecting the lives of patients.

- According to Coast’s CEO, who will testify today, Coast had a practice of voting on research protocols within 48 hours of the Board receiving them.
- One of the testimonials that Coast sent to prospective customers reads: “Thank you very much. You guys are the quickest IRB I have ever worked with and I have done this 7 years!”
- Coast even sent a coupon offering to give a free IRB review so researchers could “coast through your next study.”

After this Committee wrote to Coast IRB requesting documents associated with their approval of this fictitious study, Coast officials took pride in that they were able to discover that the study was bogus, but this was 5 months after they approved it! Coast’s CEO Mr. Dueber told our staff that within seconds they were able to determine that this was not an actual medical device and within 4 or 5 hours they determined that this was a scam. Had any of his staff done this research BEFORE they approved our bogus protocol 5 months ago, Coast IRB would not be here testifying today.

GAO’s investigation also exposed other problems with the IRB system. GAO was able to create a fictitious IRB that it registered with the U.S. Department of Health and Human Services (HHS) with no questions asked. The president of this fake IRB was this dog, Trooper, who sadly is now deceased. [Trooper didn’t know anything about protecting human subjects in testing, but for a three-legged dog, he sure could catch a Frisbee!] GAO created a fake website for Trooper’s IRB called Maryland Hause. They received real inquiries from real researchers, and actually had one research protocol submitted for review. When asked why it selected GAO’s fake IRB to review its study, a research coordinator stated that it was because of the low price and quick turn around time.

GAO’s findings raise serious questions not only about the specific IRB involved in this investigation, but with the entire system for approving experimental testing on human beings. As a society, we have a moral obligation to ensure that human testing is done in the most responsible and ethical manner. I look forward to the testimony today and hope we can discuss ways for both government and industry to fulfill this obligation.

Mr. STUPAK. I next go to the ranking member, my friend, Mr. Walden, for his opening statement, please.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. Thank you, Mr. Chairman, for convening this hearing. It is another example of the kind of investigative work that is possible when we work together in a bipartisan manner as we most always do. The subject of this hearing, the oversight of human subjects in clinical trials by Institutional Review Boards or IRBs, grew out of a drug safety investigation in the last Congress. Working together we identified what we thought might be problems in IRB oversight of clinical trials. We made a joint request to the Government Accountability Office, the GAO, to take a closer look into what was going on. Now we are here today to learn about the results of that investigation.

As we meet today, literally millions of Americans are engaged in clinical trials taking place in more than 350,000 locations across America. Right now people who have volunteered for these trials are walking into a doctor's office or a hospital or some other setting, and they are taking experimental medicines or allowing new devices to be used on their bodies so that scientists and doctors can determine whether and how a new treatment will work. Without their willingness to volunteer for a trial, all of us would not benefit from the new drugs or devices to treat illness and disease. But they volunteer believing that an independent government-sanctioned process is reviewing the protocols and products to maximize their safety.

And I have to tell you that after reading the report of the GAO that explains how easy it was for the undercover investigators to fake their backgrounds and get approval for human trials and create their own fake IRB something is horribly wrong. Mr. Dueber, I have read your testimony for today, and I find it to be the most pathetic example of trying to spin your way out of taking responsibility for a serious approval error I have ever seen. The fact that your board unanimously approved this fake company to turn fake tests using a witches' brew recipe for a gel that doesn't exist, I find to be outrageous. Two other IRBs rightfully rejected the application saying the plan was awful, a piece of junk, and the riskiest thing I have ever seen on this board.

So why did your company unanimously approve it? And would you want your family members to participate in a trial using this gel? No, rather than discuss how your board reached unanimous approval and said the gel is probably very safe and that a risk assessment is not required, you chose to attack the investigators and even called this oversight effort tyranny. Well, sir, your approach is misguided. It reminds me of the old ruse used by parents on their children to draw their attention away going, look, bright shiny object. I don't care how many bright, shiny objects you tell us to look at, your PR firm and your lawyers, to draw attention away from the real issue, your company still has to answer for this decision that would have allowed patients to spend 5 months taking a fake and potentially lethal product from a fake company with a fake doctor.

And to HHS, what in the devil is going on in your agency that allows you to think you can ignore the law and regulations regarding adequacy of IRBs and simply enter whatever is e-mailed your way and put the U.S. Government stamp of approval on an IRB? You have three federal employees signing up 300 new IRBs a month, according to the GAO, and the leadership of this agency says it is not important to follow the federal rules regarding a test of adequacy? Nobody picked up on names like Phake Medical Devices, April Phuls, Timothy Wittless, and Alan Ruse, or the town of Chetesville, Arizona? This didn't raise a flag? And yet you give out the HHS stamp of approval. It is unbelievable. Moreover, it could be lethal.

Is it any wonder the GAO says this system is vulnerable to manipulation? I understand that more than 10 years after the Inspector General's report, FDA recently announced a final rule with respect to the IRB registry system that will go into effect this summer. I am curious whether our witnesses believe this new rule will address any of the problems we will hear about today. It is our solemn duty to ensure that those who participate in clinical trials can have confidence that their safety is in trustworthy hands and that government certification means something. We want to encourage participation and support of clinical trials by protecting the integrity of these studies and strengthening the public trust. Thank you again, Mr. Chairman, for convening this hearing. I look forward to today's testimony, and I yield back my time.

[The prepared statement of Mr. Walden follows:]

Opening Statement of the Honorable Greg Walden
Ranking Member, Subcommittee on Oversight and Investigations
Hearing on "Institutional Review Boards that Oversee Experimental Human
Testing for Profit"

March 26, 2009

Thank you, Chairman Stupak, for convening this hearing.

This hearing is a great example of the type of investigative work that is possible when we work in a bipartisan fashion. The subject of this hearing — the oversight of human subjects in clinical trials by Institutional Review Boards, or "IRBs"— grew out of a drug safety investigation in the last Congress. Working together, we identified what we thought might be problems in IRB oversight of clinical trials; we made a joint request to GAO to take a closer look into what was going on; and now we are here today to learn about the results of that investigation.

As we meet today, millions of Americans are engaged in clinical trials taking place in more than 350,000 locations all across America. Right now, people who have volunteered for these trials are walking into a doctor's office and taking experimental medicines or allowing new devices to be used on their bodies so that scientists and doctors can determine whether and how a new treatment will work. Without their willingness to volunteer for a trial, all of us would not benefit from new drugs or devices to treat illness and disease.

They volunteer believing that an independent, government-sanctioned process is reviewing the protocols and products to maximize their safety.

And I have to tell you that after reading the report of the GAO that explains how easy it was for the undercover investigators to fake their backgrounds and get approval for human trials and create their own fake IRB, something is horribly wrong.

And Mr. Dueber, your testimony is the most pathetic example of trying to spin your way out of taking responsibility for a serious approval error I've ever seen. The fact that your board unanimously approved this fake company to run fake tests using a witches' brew recipe for a gel that doesn't exist is outrageous. Two other IRBs rightfully rejected the application saying the plan was "awful," a "piece of junk," and the "riskiest thing I've ever seen on this board." So, why did your company unanimously approve it? And would you want your family members to participate in a trial using this gel?

No, rather than discuss how your board reached a unanimous approval and said the gel is "probably very safe" and that a "...risk assessment is not required," you choose to attack the investigators and call this oversight "tyranny."

Well, sir, your approach is misguided. It reminds me of the old ruse used by parents on their children to draw their attention away..."LOOK...BRIGHT SHINY OBJECT!!"

No matter how many times your PR firm and you try to draw our attention away from the real issue, your company still has to answer for this decision that would have allowed patients to spend five months taking a fake, and potentially lethal, product from a fake company with a fake doctor.

And to the HHS...what in the devil is going on in your agency that allows you to think you can ignore the law and regulations governing the adequacy of IRBs and simply enter whatever is emailed your way and put the U.S. Government stamp of approval on and IRB?

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And yet, you give out the HHS stamp of approval? This is simply unbelievable. Moreover, it could be lethal.

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I understand that, more than 10 years after the Inspector General's report, FDA recently announced a final rule with respect to the IRB registry system that will go into effect this summer. I am curious whether our witnesses believe this new rule will address any of the problems we will hear about today.

It is our solemn duty to ensure that those who participate in clinical trials can have confidence that their safety is in trustworthy hands and that government certification means something. We want to encourage participation and support of clinical trials by protecting the integrity of these studies and strengthening the public trust.

I thank you again, Chairman Stupak, for convening this hearing and I look forward to today's testimony. I yield back the balance of my time.

Mr. STUPAK. Thank you, Mr. Walden. Ms. DeGette, for an opening statement, 3 minutes, please.

OPENING STATEMENT OF HON. DIANA DeGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO

Ms. DeGETTE. Thank you, Mr. Chairman. Chairman, patient safety and research situations for this committee is really like food safety. One thing you can be sure of is that a crisis is looming just around the corner. In 1999, a young man named Jesse Gelsinger died while participating in a gene therapy trial at the University of Pennsylvania. An FDA investigation concluded the scientist involved in the trial, including the lead researcher, who had a potential financial interest in the results of the trial, broke several rules of ethical conduct including inadequate informed consent procedures. In 2006 the antibiotic, Ketek, caused liver failure and death in patients who used it. An investigation showed that investigators had given fraudulent data to the FDA to gain approval of Ketek.

A whistleblower who learned of the fraud contacted the Institutional Review Board that was responsible for approval of the Ketek clinical trial, but the IRB allegedly did nothing to report the fraud and stop the use of Ketek. And now here we are again today. Research is the key to innovation and discovery including curing deadly diseases, but as this whole panel agrees, the research must be conducted ethically so that participants understand the risk and make informed decisions about volunteering. That is why we need to upgrade our entire patient protection system in this country.

Mr. Chairman, I have introduced legislation in the last 6 sessions of Congress, the Protection for Participants in Research Act, and it reforms federal regulation and oversight of research on human participants by making federal regulations applicable to all research that is in or affects interstate commerce, that strengthens the education and monitoring of Institutional Review Boards, that harmonizes FDA regulations and the common rule, the two major sets of federal regulations governing research participant protection, that strengthens protection against conflicts of interest by investigators or IRB members, that improves monitoring of research risks and reporting of adverse events and unanticipated problems.

We have reintroduced this legislation this session of Congress, and I would urge every member of this subcommittee on both sides of the aisle to look at the bill and think seriously about co-sponsoring it. The last session of Congress, we came close to passing the legislation on the suspension calendar because I think one thing we can all agree on in a bipartisan way is that we need to encourage medical experimentation but we need to do it in a way that both protects the patient and gives them informed consent about what they are getting into. Mr. Chairman, I don't want to be here for 13 hearings like we have been on food safety. I want to get this done. We have been working on it a number of years. We know the problem. We know the solutions. And I am looking forward to working with everybody on this committee to improving research so that we can have a robust system but at the same time protect the participants. Thank you, Mr. Chairman.

Mr. STUPAK. Thank you. Mr. Burgess for opening statement, please.

**OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BURGESS. Thank you, Mr. Chairman. In a surprise move, I am going to agree with the other side of the dais about the number of hearings, not wanting to have the numbers of hearings we have had on other areas before we do something. You know, today's economic environment, there is a lot of investigative activity that we could focus on, and we continue, continue, to have FDA-related hearings. I mean this is the Committee on Oversight and Investigations, not the committee to investigate the FDA. But I believe this subcommittee has some jurisdiction on what has happened with the financial services in this country, and we have had no hearings on that. Secretary Geithner might enjoy a visit to our committee and I would enjoy having the opportunity to question him. So the extent that this subcommittee has jurisdiction over the troubled asset relief program, I believe we ought to be involved.

The Department of Energy, we had two hearings in this subcommittee last Congress on the security of our national labs. I recall us having questions for the head of the Lawrence Livermore laboratory. Well, it turns out now he is just right down the street at the Department of Energy. When are we going to go have Secretary Chu in to provide answers to that questions that we couldn't get answered last fall? Instead, we are having yet another hearing on the Food and Drug Administration, an agency that we all know is in desperate shape, is broken. The morale of its workers is precariously low. We acknowledge it. We are part of the cause. It is a 20th century agency operating in a 21st century world, a world that is global, commercial, and innovative with regards to food, drugs, and medical devices, but it is regulated by an agency that is underfunded, understaffed, under supported, and what meager funds we do provide them, they have got to expend preparing for the next congressional hearing.

Now these issues relating to the Institutional Review Boards are serious. Any human subject testing should be carefully overseen by the federal government to prevent abuses. The types of products that were being discussed in the issues before us today are products that I would have used in my—might have used in my former life, so I understand the seriousness of this issue, but I can also remember back right before I started medical school hearing about the experiments going on in Tuskegee, Alabama, with the former Department of Health, Education, and Welfare and their involvement. That is why the government now has the common rule to govern 17 different departments and agencies within the federal government on human testing and why the Food and Drugs Administration has similar regulations governing human subject testing for medical devices and drugs.

There must be ongoing scrutiny of the internal review boards. We must make certain the science is unfettered and rigorous and the Office of Human Research Protection needs to have the appropriate oversight. We need to make certain that we don't politicize the process, that conflicts of interest are being avoided, and all adverse events are thoroughly evaluated and that there is a clear avoidance of the IRB shopping where an Institutional Review Board will be removed from one institution to another because the

results were not favorable. I am particularly concerned about the interaction of the common rule with the Food and Drug Administration regulations governing the investigational new drug applications. We all now the failures of the IRB and Ketek. Their failure was the impetus behind the GAO report being presented to us today regarding the review and oversight of the Institutional Review Boards.

But this is a problem that can be fixed. Let us fix it and move on to the next thing. We should hold a hearing on the entire approval process at the FDA. The IRBs, certainly they need to be investigated, the registration system, but what about the 510K exception for new drugs and the alleged revolving door where FDA employees go straight to the drug companies and then come back. We owe it to the American people. We owe it to the scientific community to fix the FDA and fix it right. Let us get on with that task. I yield back.

Mr. STUPAK. I thank the gentleman. I would also note this week you addressed to a letter to us on wanting to do hearings on medical devices with the FDA, and that is something that we are looking at closely so just so the record is clear, we will probably have more FDA hearings unfortunately. Ms. Christensen for opening statement, please.

OPENING STATEMENT OF HON. DONNA M. CHRISTENSEN, A REPRESENTATIVE IN CONGRESS FROM THE VIRGIN ISLANDS

Mrs. CHRISTENSEN. Thank you, Mr. Chairman. This is a very important hearing, and I thank you, Chairman Stupak and Ranking Member Walden for holding it. Because of the differences we have seen in response to medications and other treatments by African Americans, we, including the National Medical Association who I see in the audience, have been encouraging individuals and providers in our communities to become involved in clinical trials. I even participated in one briefly before coming to Congress. But in our community the specter of Tuskegee still looms large in our minds, and then there have been more recent incidents. I recall joining with other members of the House to stop the testing of pesticides in children, mostly African American poor children, just a few years ago.

So if we though that this was an aberration or that Tuskegee could not happen again, obviously as we try to convince our communities the GAO report tells us that we were badly mistaken. The IRB process is supposed to ensure the health and safety of individuals in clinical trials. We, who have apparently misplaced our trust in the system are outraged at the failures that are documented in the GAO report. This system needs to be fixed, and I for one cannot in good conscience encourage another person to participate in a clinical trial until it is. Thank you, Mr. Chairman. I yield back.

Mr. STUPAK. Thank you, Ms. Christensen. Mr. Gingrey, opening statement, please.

Mr. GINGREY. Mr. Chairman, thank you. Today this committee has an opportunity to make sure that Institutional Review Boards are taking every possible step to ensure the safety of those who agree to participate in biomedical research. Biomedical research and clinical trials are critical to developing and perfecting the next

generation of life saving medicine and devices. Without question, the potential benefits must outweigh the potential risks to participants. However, these individuals must also be made fully aware of the potential risks when they agree to participate. Mr. Chairman, I look forward to listening to the testimony, and I would like to reserve the balance of my time for questions, and I yield back.

Mr. STUPAK. Thank you, Mr. Gingrey. Mr. Green for opening statement, please.

**OPENING STATEMENT OF HON. GENE GREEN, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. GREEN. Thank you, Mr. Chairman. I thank you for having this hearing today on the Institutional Review Boards, the IRBs, and the federal government's oversight of these boards. IRBs were created to protect individuals from harm or death during an experiment and ensure individuals give informed consent to the researchers. IRBs are in place to minimize the risks to the subjects, that the risks of the study are reasonable in anticipation of the benefits. Protection for subjects during experimental research are vital. Unfortunately, we have two painful incidents in our past to remind us just how necessary these protections are, the formaldehyde distribution in 1960 and the Tuskegee study in 1974. Both of these incidents serve as painful reminders of the wrongdoing of researchers at the expense of the health and well-being of the subjects.

Most recent, we have the Ketek incident, which the IRB failed to investigate a whistleblower's allegations during continuing review of the application. I was on this subcommittee when we investigated Ketek and the flawed review process that enabled the drug to come to market. Several deaths have occurred during studies that received IRB approval. In recent years, many called for reforms to the IRB system. IRB regulations were created in the 1970's and have not been reformed in recent years. Currently, HHS and the Office of Human Research Protection has the jurisdiction over IRBs for studies with federal funding. FDA has jurisdiction over testing for medical devices and drugs.

HHS requires IRBs but the FDA does not. However, the FDA is developing an IRB process. There are also independent IRBs not affiliated with any institution operating in the U.S. These IRBs are associated with the industry. The GAO and HHS have issued several reports documenting problems with the current IRB process. In 1998, GAO issued several recommendations for IRB reform, and to date none of these recommendations have been adopted by HHS or FDA. I am looking forward to the testimony of the witnesses, particularly GAO, so we can see if our oversight of IRBs is adequate and whether reforms of the system need to be made. And I yield back my time.

Mr. STUPAK. Thank you, Mr. Green. Member of the subcommittee, Mr. Markey, for opening statement, please.

**OPENING STATEMENT OF HON. EDWARD J. MARKEY, A REP-
RESENTATIVE IN CONGRESS FROM THE COMMONWEALTH
OF MASSACHUSETTS**

Mr. MARKEY. Thank you, Mr. Chairman, very much. While legitimate research is vital, human experimentation must be conducted

under the highest ethical standards. This is a very important issue to me. In November of 1986, as chairman of the Energy and Commerce Subcommittee on Energy and Power, I released a report describing radiation experimentations on human subjects by American scientists between the 1940's and the 1970's. The people tested in these experiments were used as nuclear human guinea pigs to determine the effects of exposing humans to nuclear radiation. Most of those experiments provided little or no medical benefit to the patients. In many cases informed consent was not granted, yet, these individuals were asked to ingest, inhale, or be injected with radioactive materials, materials whose safety was not yet determined.

These scientists recklessly endangered human lives and much of their work was kept hidden from the public until the 1980's and 1990's. The good news is that although when I released my report in 1986 the Reagan and then Bush administrations refused to respond to it. President Clinton, in 1994, upon my urging established the Presidential Advisory Committee on Human Radiation Experiments, which issued this report which led to the strengthening of regulations for research with human subjects.

We are here today to discuss IRBs. IRB is supposed to stand for Institutional Review Board. Unfortunately, with some experiments, IRB stands for irresponsible, reckless behavior. Unscrupulous IRBs have followed lax review procedures and unethical practices when assessing the safety of clinical trial experiments. As a result, participants have been put at risk of injury or worse, death. Without proper review from IRBs, the scientific integrity of clinical research work has been compromised. This can lead to faulty evidence regarding the safety of drugs and devices, and can further endanger the safety of the public at large if these products gain approval by the FDA.

When it comes to protecting the safety of consumers, we must have the highest standards. In February of 2007 when I called on the FDA through several of my letters and a hearing by this subcommittee, and, again, Mr. Chairman, you have been a real leader on this, to answer questions regarding the safety of the antibiotic Ketek, the FDA approved Ketek partly based on fraudulent studies of its safety. Later, we found that Ketek is linked to severe liver damage and death. In this case, the IRB responsible for approving the clinical trials of Ketek ignored warnings from a whistleblower.

Mr. Chairman, you have really been a policeman, a watchdog, on this issue. This hearing is another in the long process that you have conducted, and I want to congratulate you for that. I yield back the balance of my time.

Mr. STUPAK. Thank you, Mr. Markey. Ranking member of the full committee, Mr. Barton, has joined us. Opening statement, please, Mr. Barton.

**OPENING STATEMENT OF HON. JOE BARTON, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BARTON. Thank you, Mr. Chairman. Apparently, I am still in time to do the digital transition opening statement too if that subcommittee chairman is here for this hearing. I want to echo what Congressman Markey just said about your leadership and

Mr. Walden's leadership on this issue in taking a look at the Institutional Review Boards. We are following up today on an issue that was uncovered during an investigation in the last Congress. The question is whether these Institutional Review Boards do a good job of protecting human subjects. When we started looking into this, we were concerned that some of the IRBs were not equipped to handle the amount of the complexity of the work that comes up during the clinical trials.

As a part of our subsequent investigation was an undercover work that the GAO conducted over the last year. GAO made up a supposed clinical investigator, outfitted him with a transparently suspicious resume, assigned him a fake medical license number. GAO also concocted a verifiably false company, devised med systems as a sponsor of the fake study. The study protocol was straight from the Internet, and the device, the company, and the doctor were 100 percent fictitious. Once this particular IRB learned the committee was investigating to their credit it took them less than a day to decide that something was wrong. Instead of actually doing something, they put out a news release that acted as if they had just been stung by James Bond instead of the GAO.

The IRB is here today to explain why it decided to approve the equally easy to detect fake protocol and whether it stands by that decision. I suspect that this subcommittee will have some very direct questions about the alleged science and the patently false protocol that Coast IRB rubberstamped and why it caused no apparent concern even though it had no supporting data from clinical trials and the study devised matched examples of significant risk devices on the FDA's own web site. I think we should be careful not to over emphasize or to under emphasize the significance of what this investigation has shown. Coast IRB was sloppy and/or negligent, perhaps just flat wrong, in its judgment about the protocol and the risk it posed to its study's subjects.

But, fortunately, two other IRBs that were presented with the same protocol rejected it, one without even considering it. The vast majority of clinical trials, at least I hope, are conducted without harm to patients. Even so, I am bothered by the fact that two of the IRBs that GAO investigated and the other IRBs who advertised in trade magazines and on the Internet seemed to focus on the speed of their review and the guarantees of a quick turnaround time. In some of those ads, patient protection and safety seem almost like an after thought. The bigger issue today may not be that one IRB made a grade error and then tried to throw attention elsewhere, but that the current set of regulations does little to prevent such an error. That is our job if we need to review those regulations.

We need to take a close look at those regulations and ask whether they are meaningful in the current research and clinical trial environment. Current regulations require that an IRB must make a number of determinations before approving a protocol, including that risks are minimized to the patient and that the patient has knowingly consented to participating in the study. But as GAO and the HHS Office of Inspector General have been reporting for years, there is basically no test that an IRB must pass before it opens for business to show that it is qualified to review such clinical trials.

It is frustrating that the same problems keep popping up. These are problems that the GAO and the Inspector General have discussed in reports issued as long as 10 years ago.

I know that the FDA recently announced a rule that would require IRBs to register with the FDA, but again that was a reform that was called for years ago, and I don't think that this rule would have made much difference with regard to solving the problems that the GAO has identified in its most recent undercover investigation. By putting the GAO findings in proper context, we can strengthen bio-medical research and innovation. If the public sees that our committee and federal agencies are ensuring that the research committee is looking out for the folks here confidence in clinical trials will be boosted and participation will increase. This should be a very meaningful hearing if we keep our discussion in perspective. I want to thank our witnesses for testifying today, and, again, you, Mr. Chairman, and Mr. Walden for leading on this issue. I yield back.

Mr. STUPAK. Thank you, Mr. Barton. That concludes the openings statements of members of the subcommittee. We have out first panel of witnesses before us. The panel that we have is Mr. Gregory Kutz, who is the Managing Director of Forensic Audits and Special Investigations at the Government Accountability Office, GAO, Dr. Jerry Menikoff, who is the Director of the Office for Human Research Protections at the Department of Health and Human Services, Dr. Joanne Less, who is the Director of the Good Clinical Practice Program at the Food and Drug Administration, and Mr. Daniel Dueber, who is the Chief Executive Officer at Coast IRB, LLC.

It is the policy of this subcommittee to take all testimony under oath. Please be advised that you have the right under rules of the House to be advised by counsel during your testimony. Do you wish to be represented by counsel? If so, would you have them—would you state your counsel's name? Mr. Kutz. Dr. Less. Dr. Menikoff. Mr. Dueber.

Mr. EMORD. Jonathan Emord.

Mr. STUPAK. OK. During your testimony, if you want to stop and confirm with that, that will be fine. He cannot testify but he can give you advice. That is fine. It is the policy of this subcommittee to take all testimony under oath, so I am going to ask you to please rise, raise your right hand, and take the oath.

[Witnesses sworn.]

Mr. STUPAK. Let the record reflect the witnesses replied in the affirmative. They are now under oath. We will proceed with your opening 5-minute statement. Mr. Kutz, we will start with you, please, sir.

TESTIMONY OF GREGORY KUTZ, MANAGING DIRECTOR, FORENSIC AUDITS AND SPECIAL INVESTIGATIONS, GOVERNMENT ACCOUNTABILITY OFFICE; JERRY MENIKOFF, M.D., DIRECTOR, OFFICE FOR HUMAN RESEARCH PROTECTIONS, DEPARTMENT OF HEALTH AND HUMAN SERVICES; JOANNE LESS, DIRECTOR, GOOD CLINICAL PRACTICE PROGRAM, FOOD AND DRUG ADMINISTRATION; AND DANIEL DUEBER, CHIEF EXECUTIVE OFFICER, COAST IRB, LLC

TESTIMONY OF GREGORY KUTZ

Mr. KUTZ. Mr. Chairman and members of the subcommittee, thank you for the opportunity to discuss Institutional Review Boards. Our investigation relates principally to private IRBs that authorize human subject testing. Today's testimony highlights the results of our investigation of the IRB system. My testimony has 2 parts. First, I will provide some very brief background, and, second, I will discuss the results of our investigation. First, as several of you have mentioned, federal regulations governing human subject testing evolved from society's horrified reaction to several cases.

For example, there were the forced medical experiments on countless Holocaust victims. In the U.S., we had the 40-year Tuskegee study. In this case, hundreds of poor, mostly illiterate African American men, were not properly treated for syphilis so that the effects of this disease could be studied. Today, IRBs play a critical role in the safety and protection of human subjects. With this background in mind, let me move on to our results. Our investigation found that the current system is highly vulnerable to unethical or incompetent actors. We tested the IRB system with 2 separate but related undercover operations. The objective of the first operation was to see if an actual IRB would authorize our bogus medical device company to conduct human subject testing.

The objective of our second operation was to determine whether a real medical research company would hire our bogus IRB. If successful, this would show that the bogus IRB could have authorized human subject testing. First, our bogus medical device protocol was approved by a real IRB even though we had no medical expertise. Our bogus device, which we called adhesive block, was a post-surgical healing device for women that matched several FDA descriptions of a significant risk device. We created our protocol and fictitious device using information that was publicly available and on the Internet. The monitors show excerpts from the IRB board meeting where our protocols were unanimously approved and adhesive block was referred to as being probably very safe.

As shown on the monitors, some due diligence would have shown a mailbox as our suite or office, a fictitious lead researcher with a fabricated medical license and resume, a fabricated FDA marketing approval for our device, and a cell phone as the only number we provided. The next picture on the monitor shows a coupon that this IRB provided which got our attention. Given that we are dealing with experimental research on human beings, we were surprised that anybody would offer discount coupons for this service. This IRB is no fly by night operation. They are currently the IRB of

record for over 70 federally-funded projects, and according to their own press release have overseen thousands of trials.

Two other IRBs we sent these very same protocols to had a very different response. The monitor shows examples of their comments, including this protocol was awful and a piece of junk, the riskiest thing I have ever seen, the odds of approval were 0 percent, and my favorite comment, if somebody approves it, oh, boy. For the IRB that approved our study, the only due diligence they appeared to perform was after they received a letter from this subcommittee. After receiving this letter, the IRB was able to determine, for example, that our lead researcher and FDA marketing approval were, in fact, bogus. However, this IRB had already approved our bogus device for human subject testing 4 months before receiving your letter.

For our second operation, we created a bogus private IRB. Once again, we used phony company officials and a mailbox as our business address. We registered our IRB on line with HHS and created a web site that looked like the web sites that other IRBs used. Then we went fishing. We advertised our services on the Internet and in newspapers to see if a real researcher or researchers would contact us. The monitors show our advertisements. Notice that we emphasized the speed of our reviews, our HHS approval, and guaranteed results. We did refrain from offering discount coupons as part of our advertising campaign.

In response to these ads, our bogus IRB received protocols from one company and inquiries from five others. The company sending us its protocols was seeking approval to add a new test site for on-going trials. Our bogus IRB, which as I mentioned had absolutely no medical expertise, could have authorized human subject testing at this site. However, we told this company that we couldn't review their protocols because we were experiencing significant financial problems due to the current economic crisis. In conclusion, every year millions of Americans submit themselves to experimental research. These people are among our nation's poorest and most vulnerable. I can't tell you whether our 2 undercover successful tests are isolated cases or the tip of the iceberg.

What I can tell you is given the history of human subject testing, it is hard to believe that anybody could be comfortable with the integrity of the current system. Mr. Chairman, that ends my statement and I look forward to your questions.

[The prepared statement of Mr. Kutz follows:]

United States Government Accountability Office

GAO

Testimony
Before the Subcommittee on Oversight
and Investigations, Committee on Energy
and Commerce, House of Representatives

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**HUMAN SUBJECTS
RESEARCH**

**Undercover Tests Show the
Institutional Review Board
System Is Vulnerable to
Unethical Manipulation**

Statement of Gregory D. Kutz, Managing Director
Forensic Audits and Special Investigations



March 26, 2009

HUMAN SUBJECTS RESEARCH

Undercover Tests Show the Institutional Review Board System Is Vulnerable to Unethical Manipulation

Highlights of GAO-09-448T, a testimony before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

Millions of Americans enroll in clinical studies of experimental drugs and medical devices each year. Many of these studies are meant to demonstrate that products are safe and effective. The Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) are responsible for overseeing aspects of a system of independent institutional review boards (IRB). IRBs review and monitor human subjects research, with the intended purpose of protecting the rights and welfare of the research subjects.

GAO investigated three key aspects of the IRB system: (1) the process for establishing an IRB, (2) the process through which researchers wishing to apply for federal funding assure HHS their human subjects research activities follow ethical principles and federal regulations, and (3) the process that medical research companies follow to get approval for conducting research on human subjects.

GAO investigated these three aspects of the IRB system by creating two fictitious companies (one IRB and one medical device company), phony company officials, counterfeit documents, and a fictitious medical device.

To view the full product, including the scope and methodology, click on GAO-09-448T. For more information, contact Gregory D. Kutz at (202) 512-6722 or kutzg@gao.gov.

What GAO Found

The IRB system is vulnerable to unethical manipulation, which elevates the risk that experimental products are approved for human subject tests without full and appropriate review. GAO investigators created fictitious companies, used counterfeit documents, and invented a fictitious medical device to investigate three key aspects of the IRB system. These are the results:

Establishing an IRB. GAO created a Web site for a bogus IRB and advertised the bogus IRB's services in newspapers and online. A real medical research company contacted the bogus IRB to get approval to join ongoing human trials involving invasive surgery—even though GAO's investigators had no medical expertise whatsoever. Since the transaction involved privately funded human subjects research and did not involve any FDA-regulated drugs or devices, GAO's bogus IRB could have authorized this testing to begin without needing to register with any federal agency.

Obtaining an HHS-approved assurance. GAO also registered its bogus IRB with HHS, and used this registration to apply for an HHS-approved assurance for GAO's fictitious medical device company. An assurance is a statement by researchers to HHS that their human subjects research will follow ethical principles and federal regulations, which is required before researchers can receive federal funding for the research. On its assurance application, GAO designated its bogus IRB as the IRB that would review the research covered by the assurance. Even though the entire process was done online or by fax—without any human interaction—HHS approved the assurance for GAO's fictitious device company. With an HHS-approved assurance, GAO's device company could have applied for federal funding for human subjects research.

Obtaining IRB approval for human testing. GAO succeeded in getting approval from an actual IRB to test a fictitious medical device on human subjects. GAO's fictitious device had fake specifications and matched several examples of "significant risk" devices from FDA guidance. The IRB did not verify the information submitted by GAO, which included false information that FDA had already cleared GAO's device for marketing. Although records from this IRB indicated that it believed GAO's bogus device was "probably very safe," two other IRBs that rejected GAO's protocol cited safety concerns with GAO's device. No human interaction with these IRBs was necessary as the entire process was done through e-mail or fax. GAO's bogus IRB mentioned above also could have approved the fictitious protocol, which shows the potential for unethical manipulation in the IRB system.

GAO briefed HHS officials on the results of its investigation. The director of OHRP stated that, when reviewing assurance applications, HHS does not consider whether IRBs listed on the applications are adequate—even though HHS is required to do so by law. In addition, HHS officials stated that the department does not review assurance applications to determine whether the information submitted by applicants is factual.

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to discuss our investigation of vulnerabilities in the institutional review board (IRB) system. An IRB is an entity formally designated to review and monitor biomedical and behavioral research in clinical trials involving human subjects, with the intended purpose of protecting the rights and welfare of the research subjects. Each year, millions of Americans enroll in clinical trials of experimental drugs and medical devices conducted in over 350,000 locations throughout the United States. Many of these clinical trials are meant to demonstrate that products are safe and effective, and are sometimes conducted or sponsored by private pharmaceutical and medical device manufacturers. Although research subjects are required to give consent prior to their participation in these studies, a patient has the expectation that the product being tested presents a risk that is reasonable in relation to any anticipated benefits, and that all risks are fully disclosed. The Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) are responsible for overseeing aspects of the system of IRBs.

Unfortunately the IRB system sometimes fails to protect research subjects. For example, in 2002, a 47-year-old man died after his heart stopped beating while participating in an experimental trial of antipsychotic medication at a Texas research center. Before his death, the man spent 22 days suffering from fever, severe diarrhea, a rapid heartbeat, and kidney failure while under the care of researchers. The warning label for the experimental medication listed some of these serious side-effects and other signs of heart failure, but the IRB failed to ensure the risks were communicated to participants at the outset of the trial. During the clinical trial, the lead researcher continually delegated control of the clinical trial to a man who was unlicensed to practice medicine in the United States. In its follow-up investigation after the death, the FDA noted that the IRB repeatedly violated regulations governing the proper conduct of clinical trials and did not adequately supervise the clinical trial.

Most IRBs were historically located at academic institutions. However, independent IRBs are playing an increasingly prominent role in the protection of human research subjects.¹ Questions have been raised as to

¹For the purposes of this testimony, we define an independent IRB as a private IRB that is not part of the same organization as the entity whose research is under the IRB's review.

whether all of these independent IRBs exercise effective due diligence in reviewing research protocols. Given the importance of IRBs in protecting human health and safety, you asked us to perform undercover tests to find out whether the IRB system is vulnerable to unethical manipulation. Specifically, we investigated three key aspects of the IRB system: (1) the process for establishing an IRB, (2) the process through which researchers who wish to apply for federal funding assure HHS that their activities related to human subjects are guided by ethical principles and federal regulations, and (3) the process that medical research companies follow to get approval for conducting research on human subjects.

To investigate the process for establishing an IRB, we created a fictitious IRB with phony company officials and only a mailbox for a business location. We then registered our fictitious IRB with HHS using its online registration form. We created a Web site that resembled those of other actual IRBs. We also advertised the services of our bogus IRB in various media, such as Web sites dedicated to the clinical trials industry and newspapers, in an attempt to persuade legitimate medical researchers to send protocols to our bogus IRB. In our advertisements, we stated that we were "HHS approved," in reference to our bogus IRB's registration with HHS. In addition, we emphasized the speed of our review process ("Fast Approval!"), customer service, and flexibility to customer needs in order to make our IRB look as attractive as possible.²

To investigate the process through which human subjects researchers who wish to apply for federal funding assure HHS that their activities related to human subjects are guided by ethical principles and federal regulations, we attempted to file a Federalwide Assurance for the Protection of Human Subjects for Institutions Within the United States (assurance) application using HHS's online application form, under the guise of a fictitious medical device company. We created a fictitious medical device company with phony company officials and only a mailbox for a business location, claiming that this mailbox was the facility where we intended to conduct

²Concerns about the speed of IRB reviews go back more than a decade. We noted in a 1996 report that some IRBs spent only 1 or 2 minutes on each review, often focusing mostly on reviewing the proposed research study's informed consent forms. See GAO, *Scientific Research: Continued Vigilance Critical to Protecting Human Subjects*, GAO/HEHS-96-72 (Washington, D.C.: Mar. 8, 1996). In addition, the HHS Office of Inspector General noted in 1998 that IRBs reviewed too many research protocols too quickly. See Department of Health and Human Services, Office of Inspector General, *Institutional Review Boards: A Time for Reform*, OIG-01-97-00193 (Washington, D.C.: Department of Health and Human Services, Jun. 1998).

our human subjects testing. As part of filing for an assurance, we were required to submit information about the IRB that would be reviewing our research protocol, for which we listed our fictitious IRB.

To investigate the process that medical research companies follow to get approval for conducting research on human subjects, we created a research protocol for a fictitious medical device with no proven test history and bogus specifications, using information publicly available on the Internet. We designed our protocol so that it would contain vague information about certain aspects of our proposed study. Our fictitious device was a post-surgical healing device for women that matched multiple examples of "significant risk"³ devices provided in publicly available FDA guidance. Our bogus medical device company then approached three actual, independent IRBs with information about our device and indicated that we wanted to submit our protocol for review and approval to conduct human testing. We selected these three IRBs by conducting a search online to identify independent IRBs, and then choosing three that we determined had less burdensome initial paperwork requirements than other IRBs for protocol submission. We fabricated additional documents requested by the IRBs for their initial review of our protocol, such as a curriculum vitae (CV) detailing our fictitious researcher's educational and professional experience,⁴ and a medical license for our fictitious researcher. We created these counterfeit documents by using information found online and with commercially available hardware, software, and materials. After concluding the undercover portion of our investigation, we contacted two of the three IRBs to obtain information about their review process.

We performed this investigation from January 2008 to March 2009 in accordance with quality standards for investigations prescribed by the President's Council for Integrity and Efficiency.

³The FDA draws a distinction between "significant risk" and "non-significant risk" medical devices. A significant risk device, defined in 21 C.F.R. § 812.3(m), is one that "presents a potential for serious risk to the health, safety, or welfare of a subject"; a non-significant risk device does not present such a danger. For a significant risk device, the sponsor must submit an Investigational Device Exemption application to the FDA for approval before beginning clinical trials. For a non-significant risk device, the clinical trial must be approved by an IRB before it begins, but FDA approval is not necessary.

⁴A curriculum vitae generally provides information on a person's education, employment experience, professional memberships, publications, and other qualifications for employment.

Summary

Our investigation shows that the IRB system is vulnerable to unethical manipulation, particularly by companies or individuals who intend to abuse the system or to commit fraud, or who lack the aptitude or qualifications to conduct and oversee clinical trials. This vulnerability elevates the risk that experimental products are approved for human subjects testing with little or no substantive due diligence. We investigated three key aspects of the IRB system using fictitious companies, phony company officials, counterfeit documents, and a fictitious medical device. All communications and information submissions were conducted through the Internet or by fax. As a result, our investigators were never exposed to real-time activities, such as telephone conversations, face-to-face meetings, or site inspections, which would have revealed their lack of expertise, lack of an actual facility, and other fraudulent representations. The results of our investigation are as follows:

- Our bogus IRB received a research protocol and related materials from a real company that was seeking our IRB's approval to add one of its clinics as a new test site for ongoing human trials involving invasive surgery. Our bogus IRB could have authorized human subjects testing to begin at this new test site without needing to register with any federal agency, since the transaction involved a company conducting privately funded research and did not involve any FDA-regulated products.⁵ We also registered our bogus IRB with HHS, after which HHS provided us with a registration number and listed our bogus IRB in its online directory of registered IRBs that review federally funded research. Our only communication with HHS as part of registering our IRB was through an online registration form, with no human interaction. The IRB registration process is meant to collect data that HHS uses during the subsequent assurance approval process. As such, HHS is not required to verify the information it receives during the IRB registration process.
- HHS approved our application for an assurance, submitted by a fictitious medical device company. An assurance is required for researchers to receive federal funding from HHS for research involving human subjects testing, and is also used by other federal agencies in their funding approval process. To obtain an assurance, HHS requires researchers to designate, among other things, one or more IRBs to

⁵After we received the protocol and related materials from the real medical research company, we notified it that we were unable to serve its business needs and destroyed the documents it sent us.

review the research covered by the assurance. We successfully used our bogus IRB to obtain HHS approval for an assurance on behalf of our fictitious medical device company, which would have allowed our fictitious medical device company to apply for federal funding for human subjects research. HHS provided us with an assurance number and listed our bogus company in its online directory of approved assurances, thereby helping our fictitious medical device company appear legitimate when we submitted a bogus research protocol to real IRBs, as described below. All contact with HHS was performed through an online application form or by fax.

- One of three IRBs approved our bogus research protocol for human subjects testing after only minor edits to our submission materials, even though we were a bogus company with falsified credentials and an unproven medical device. When we provided the IRB (IRB 1) with bogus information that FDA had already cleared our device for marketing, it did not attempt to verify this information. A search of FDA's online database would have shown no evidence that FDA ever cleared the device for marketing. The remaining two IRBs (IRB 2 and IRB 3) provided us with such thorough comments on our testing protocol and submission materials that we determined we did not have the technical expertise or resources to address their questions and gain approval. For example, IRB 2 noticed that our fictitious protocol mentioned previous testing of the device performed on animals, and requested that we provide a copy of the results from the fictitious animal testing. IRB 3 requested that we send it a copy of the diagram that our bogus researcher would use to record incision lines he made as part of the surgery involved in our fictitious study. All of our communications with the IRBs during their review of our protocol were done by e-mail or fax. After submitting the protocols, we obtained meeting minutes for IRB 1 that showed its board members thought our bogus protocol was "probably very safe" and voted unanimously to approve it. However, in follow-up calls to the two other IRBs, an employee of IRB 2 said the protocol was "awful" and called it "junk." A board member of IRB 3 said it was the "riskiest thing I've ever seen on this board" and indicated that IRB 3's board voted unanimously to reject the protocol. If we had been a real medical device company, we could have used the IRB approval we received to test our device on human subjects even though our research staff had falsified credentials and no research experience.⁶ We also could have

⁶We voluntarily withdrew our protocol from consideration by the two IRBs that rejected our initial proposal, before they conducted any additional review.

used our bogus IRB mentioned above to approve our fictitious protocol, which shows the potential for unethical manipulation in the IRB system.

We briefed HHS officials on the results of our investigation. They told us that HHS does not review IRB registrations or assurance applications to assess whether the information submitted is factual. Moreover, although HHS is required by law to consider the adequacy of IRBs listed on assurance applications when reviewing applications,⁷ the director of OHRP stated that his office would require more staff to do so. HHS officials also stated that the assurance process is not a meaningful protection against unethical manipulation. The director of OHRP acknowledged, however, that an HHS-approved assurance can lend credibility to a company because it means that HHS has recognized that company.

Background

The Secretary of HHS has issued regulations that form the "Federal policy for the Protection of Human Subjects."⁸ This policy is often referred to as the "Common Rule" because 17 other federal agencies that conduct, support, or regulate human subjects testing now follow some form of the policy.⁹ The Common Rule lays out the basic policies that should govern any research involving human subjects that is approved, funded, or conducted by the agencies that follow the Common Rule, as well as by all entities that need these agencies' approval of their human subjects research.

Much of the Common Rule focuses on the role of IRBs in the testing process, as IRBs are the primary oversight mechanism for human testing. For example, the policy specifies that there must be at least five members of an IRB, with varying backgrounds, who are sufficiently qualified

⁷45 C.F.R. § 46.103(d).

⁸56 Fed. Reg. 28003 (Jun. 18, 1991).

⁹These other agencies are: Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, U.S. Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans Affairs, Environmental Protection Agency, National Science Foundation, Department of Transportation, Central Intelligence Agency, Social Security Administration, and Department of Homeland Security.

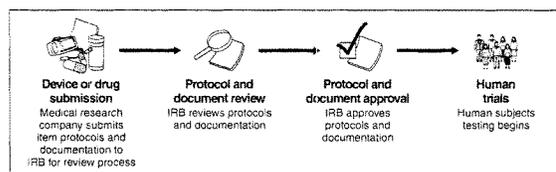
through experience, expertise, and diversity. The IRB must include members who have the professional competence to review the specific research activities being considered, as well as members with an understanding of a testing entity's internal protocols, the applicable law, and standards of professional conduct. Furthermore, among other requirements, the IRB should have members of mixed gender and mixed professions; should include at least one member with a scientific background and one with a nonscientific background; and should not have any members with a conflict of interest with the project being reviewed.

The IRB review process is intended to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. IRBs have the authority to approve, require modifications in, or disapprove proposed research. Figure 1 below provides a simplified illustration of the IRB approval process for human subjects research protocols. By law, clinical trials of experimental medical devices and drugs involving human subjects cannot begin until an IRB has approved the research protocol and any changes requested by the IRB have been made. To approve a research proposal, IRBs must determine that the following requirements are satisfied:

- risks to research participants are minimized;
- risks to research participants are reasonable in relation to any anticipated benefits, and to the importance of the knowledge that the research might produce;
- informed consent will be sought from each prospective study participant or the participant's authorized representative; and
- there are adequate provisions in place to protect research participants' privacy and to maintain the confidentiality of research data.¹⁰

¹⁰45 C.F.R. § 46.111, for HHS research, and 21 C.F.R. § 56.111, for FDA-regulated product research, describe these and other requirements for IRB approval of proposed research.

Figure 1: IRB Approval Process for Research Protocols Involving Human Subjects (Simplified)



Source: GAO.

Note: FDA may have oversight functions in this process, depending on the risk level of the device or drug under review and other factors. However, the graphic is intended to provide a simplified illustration of the interaction between an IRB and a medical research company seeking to obtain the IRB's approval for an experimental drug or device.

When seeking to obtain research participants' informed consent to participate in a study, researchers must make sure they offer the potent participants sufficient opportunity to consider whether or not to participate without undue influence or possibility of coercion. In addition, consent forms must contain language that is easily understood, and cannot contain any language that causes or appears to cause the participants to waive their legal rights, or that minimizes or appears to minimize the liability for negligence of the researcher and the sponsors of the research. In addition to reviewing proposed research protocols, IRBs are responsible for conducting continuing review of research at least once a year, or more frequently if the research represents a higher degree of risk to the human research subjects.

IRBs also play a central role in the process by which entities apply for federal funding for human subjects research. An entity must have an approved assurance in order to receive federal funding for research involving human subjects testing from HHS and other federal agencies. An assurance is basically a declaration submitted by an entity engaged in human subjects research that it will comply with the requirements for the protection of human subjects under 45 C.F.R. Part 46. HHS has jurisdiction over human subjects research that is supported through federal funding, and approves assurances for federalwide use.¹¹ As such, other federal

¹¹Federal funding includes grants, contracts, or cooperative agreements under the Public Health Service Act (codified as amended in scattered sections of 42 U.S.C. chapter 6A).

agencies that have adopted the Common Rule may rely on an assurance from HHS for any human subjects research they sponsor. To obtain an assurance, HHS requires an entity to declare to HHS that its activities related to human subjects are guided by ethical principles and federal regulations—the Common Rule—and to designate one or more IRBs to review the research covered by the assurance. In order for the application for assurance to be approved by HHS, all IRBs listed on the application are required to be registered with HHS. IRB registration involves providing HHS with basic information about the IRB, such as the name and contact information for the organization operating the IRB and for its head official, and the names and qualifications of its board members. In evaluating an application to determine whether or not to approve an assurance, HHS is required to consider, among other things, the adequacy of the proposed IRB in relation to the research activities of the entity that submitted the assurance.¹²

Results of Investigation

Establishing an IRB

We succeeded in getting a real company to send a research protocol and related materials to our bogus IRB for its review. As mentioned above, we created a Web site for our bogus IRB that resembled those of actual IRBs, and then advertised the services of our bogus IRB online and in newspapers to attempt to persuade legitimate medical researchers to send protocols to us. In our advertisements, we stated that we were “HHS approved,” in reference to our bogus IRB’s registration with HHS. We also sought to make our IRB look as attractive as possible by emphasizing the speed of our review process (“Fast Approval!”) and flexibility to customer needs. The company that sent materials to us was seeking our bogus IRB’s approval to add one of the company’s clinics as a new test site for ongoing human trials involving invasive surgery. Our bogus IRB could have authorized human subjects testing to begin at this new test site—even though it was a fictitious IRB, with no medical research expertise whatsoever. Moreover, because this transaction involved a company conducting private (i.e., not federally funded) research, and did not involve any FDA-regulated products, our bogus IRB could have approved

¹²45 C.F.R. § 46.103(d).

the research to begin without needing to register with any federal agency.¹³ We also received inquiries from five other real companies, which expressed interest in our bogus IRB's services. However, none of these five companies submitted any materials for us to review.

All IRBs that review federally funded human subjects research are required to be registered with HHS.¹⁴ After we registered our bogus IRB with HHS, HHS provided us with a registration number and listed our bogus IRB in its online directory of registered IRBs that review federally funded research. Our only communication with HHS as part of registering our IRB was through an online registration form, with no human interaction. The IRB registration process is meant to collect data that HHS uses during the subsequent assurance approval process. As such, HHS is not required to verify the information it receives during the IRB registration process. However, our investigation of the assurance process, as described below, shows the importance of IRB registration data as they relate to HHS's evaluation of assurance applications. Moreover, if our bogus IRB had been an actual IRB that did not intend to review federally funded human subjects research, it would not have been required to submit any registration information. IRBs that intend to review privately funded human subjects research are not currently required to register with HHS or any other federal agency, although recently implemented regulations will change this as of July 2009.¹⁵

HHS's Federalwide Assurance Process

We found that the process for obtaining HHS approval for an assurance lacks effective controls. As mentioned above, we formed a fictitious medical device company with phony company officials and a mailbox for

¹³As mentioned above, after we received the protocol and related materials from the real medical research company, we notified it that we were unable to serve its business needs and destroyed the documents it sent us.

¹⁴While the registration requirement is currently only HHS policy, HHS recently issued a final rule that will require registration by formal regulation. This regulation, effective July 14, 2009, also expands the amount of data an IRB is required to provide during the registration process. 74 Fed. Reg. 2399 (Jan. 15, 2009).

¹⁵FDA regulations cover some human subjects research that involves experimental drugs or medical devices, even though IRBs reviewing the research are not required to register with any agency. However, FDA does not currently maintain a comprehensive list of all IRBs involved in testing experimental drugs or devices on human subjects. On January 15, 2009, FDA issued a final rule that requires all IRBs reviewing products that fall under FDA regulations to register with HHS. This rule is effective on July 14, 2009. 74 Fed. Reg. 2358 (Jan. 15, 2009).

its business location—where human subjects research would supposedly be conducted. We then submitted an application to HHS for its approval of an assurance on behalf of our fictitious medical device company. As part of the application, we named our bogus IRB as the IRB responsible for reviewing the research covered by the assurance. HHS approved our assurance application, provided us with an assurance approval number, and listed our bogus medical device company in its online directory of approved assurances. Our only communication with HHS as part of this application was through an online application form and a faxed signature to complete the application. We did not have any real-time contact with HHS, whether by telephone, in person, or through a site visit.

We do not know what verification HHS performed, if any, in its review of our assurance application. However, if HHS had performed basic screening of the assurance application, HHS would have found discrepancies that would have warranted further investigation, such as the fact that we used only a mailbox as our business location. As mentioned above, in evaluating an application to determine whether or not to approve an assurance, HHS is required to consider the adequacy of any IRB designated on the application, as the IRB will be responsible for overseeing the research activities of the entity that submitted the assurance application. By approving our assurance application, HHS essentially deemed our bogus IRB as adequate to oversee human subjects research, as conducted by our fictitious medical device company. Moreover, by obtaining an approved assurance from HHS, our fictitious medical device company can apply for federal research funding from HHS or other federal agencies.¹⁶ In addition, we used the assurance approval to boost the credibility of our fictitious medical device company by posting our assurance number on the fictitious medical device company's Web site.

The IRB that approved our fictitious medical device protocol, as discussed below, is listed on HHS's Web site as being involved in more than 70 assurances on behalf of actual medical researchers. Each of these assurances is a first step for the medical researcher to apply for federal

¹⁶Although assurance approval from HHS allows us to apply for federal funding for our research, it does not necessarily mean that we would have been awarded such funding. However, as our investigation was designed to test HHS's controls during its process for evaluating assurance applications, we determined that the actual process of applying for federal funding for human subjects research was beyond the scope of our investigation.

funding for human subjects research, with this IRB formally designated to oversee the research.

IRBs' Research Protocol Approval Process

We were able to get an actual IRB to approve a fictitious protocol for human subjects research, which raises concerns that other IRBs may conduct protocol reviews without exercising due diligence, thereby exposing research volunteers to significant risk. For this test, we created a research protocol for a fictitious medical device with no proven test history and bogus specifications, and sent the protocol to three actual, independent IRBs under the guise of the medical device company we created for obtaining an assurance from HHS in our second test, as mentioned above. Our protocol offered only vague information about certain aspects of our proposed study and was designed using information publicly available on the Internet. As mentioned above, our fictitious device was a post-surgical healing device for women that matched multiple examples of "significant risk" devices provided in FDA guidance. In addition, we fabricated additional documents we needed to submit along with our protocol, such as a CV detailing the educational and professional experience of a fictitious researcher at our company, and a bogus medical license for the researcher. We succeeded in getting our fictitious protocol approved by an IRB, even though we were a bogus company with falsified credentials and an unproven medical device. If we had been a real medical device company, we could have begun testing our "significant risk" experimental device on actual human subjects. We also could have used our bogus IRB mentioned above to approve our fictitious protocol. This shows the potential for unethical manipulation in the IRB system.

The IRB that approved our bogus research protocol (IRB 1) required only minor edits to our submission materials, and did not verify that the information contained in our protocol and related materials was correct or authentic, or even that our medical device company actually existed. For example, we provided IRB 1 with bogus information that FDA had already cleared our device for marketing because our device was found to be

substantially equivalent to an existing, legally marketed device.¹⁷ IRB 1 did not attempt to verify this information even though a quick check of FDA's online database would have shown no evidence that FDA had ever cleared our device. By taking advantage of this lapse, our investigators—who lacked technical expertise in this subject—bypassed any requirement to develop a risk assessment for a device that, under normal circumstances, would be considered “significant risk” according to FDA guidance. Meeting minutes from IRB 1's board meeting show that it accepted the bogus information about FDA clearance of our device as evidence that our device did not require any further risk assessment. See figure 2 below.

Figure 2: Excerpts from IRB 1's Board Meeting Minutes, during Review of Fictitious Medical Device Protocol

B) NEW SPONSOR SUBMISSIONS		Excerpts from meeting minutes 1. "...risk assessment is not required." 2. Unanimous approval of item with no dissenting votes (7/7) 3. Device referred to as "...probably very safe..."
1) Medical Device Studies (a) Device [redacted] Study of Safety and Efficacy of [redacted]		
1. [Note: This Device falls under a 510k and risk assessment is not required.]		
(c) For Review: Protocol Version [redacted]		
2. [redacted] • Decision/Vote: Approve # Voting: 7 # For: 7 # Against: 0 # [Abstain/Recuse]: 0 Names(s): [Enter member's name]		
3. [Device] is probably very safe: this is a pilot study & first-time use in humans.		

Source: IRB 1.

¹⁷FDA's 510(k) premarket notification process includes a determination of whether each new device (1) has the same intended use as an existing, legally marketed device, and (2) the new device has the same technological characteristics as the existing, legally marketed device, or has different technological characteristics and submitted information shows that the new device is as safe and effective as the existing device. If FDA determines that the new device is substantially equivalent to a legally marketed device, the manufacturer may market it immediately. For more information about the 510(k) process and the more stringent premarket approval process, see GAO, *Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process*, GAO-09-190 (Washington, D.C.: Jan. 15, 2009).

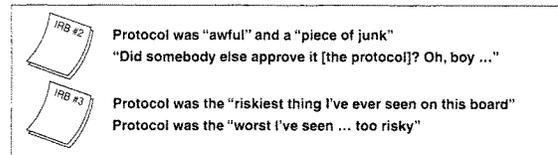
IRB 1 "conditionally approved" our protocol after a full board review, but requested that we modify our informed consent form for study participation in order to make the language understandable at a fifth-grade reading level. We modified our informed consent form as requested by using medical information found on the Internet, after which the board members of IRB 1 voted unanimously to approve our fictitious medical device protocol (see fig. 2 above). IRB 1 approved our fictitious protocol, thereby authorizing us to begin human testing, after only contacting us by e-mail or fax, and never by telephone or in person. IRB 1's board meeting minutes indicate that it believed our device was "probably very safe," as shown in figure 2 above. Although our protocol mentioned fictitious animal studies that we conducted on our device to ensure its safety, IRB 1 approved our protocol without ever seeing proof of these studies or any other evidence that our device was reasonably safe for use in human subjects. On its Web site, IRB 1 advertises the speed of its reviews and states that it performs a "triple check" for quality. IRB 1 has approved research protocols for experimental drugs tested by major pharmaceutical companies.

The remaining two IRBs (IRB 2 and IRB 3) provided feedback on our protocol that was so extensive we determined we did not have the technical expertise or resources to gain approval. The extensive nature of the feedback IRB 2 and IRB 3 provided on our initial submission materials indicated that they follow a much more thorough review process than IRB 1, which approved our protocol. For example, IRB 2 noticed that our fictitious protocol mentioned previous testing of the device performed on animals, and requested that we provide a copy of the results from the fictitious animal testing. In addition, IRB 3 requested that we send it a copy of the diagram that our bogus researcher would use to record incision lines he made as part of the surgery involved in our study, and raised a number of questions about the timing and locations involved in our fictitious testing. The documents and information that IRB 2 and IRB 3 requested would have taken extensive time and research to fabricate, and demanded a level of technical expertise that we did not possess. IRB 1 approved our protocol without obtaining any of the additional information requested by IRB 2 and IRB 3.¹⁵ Our contacts with IRB 2 and IRB 3, during their review of our protocol, were done entirely by e-mail.

¹⁵As mentioned above, we voluntarily withdrew our protocol from consideration by the two IRBs that rejected our initial proposal, before they conducted any additional review.

We later interviewed representatives from IRB 2 and IRB 3 to obtain additional details about why they did not approve our protocol. Representatives from both IRBs expressed concern that our protocol did not contain adequate information about the safety of our fictitious medical device. For example, the manager of IRB 2 said that she worried that our device could cause infection in patients, or possibly even cause patients to develop sepsis.¹⁹ In addition, a board member from IRB 3, who claimed to have 15 years of experience reviewing research protocols with this IRB, stated that our protocol lacked any evidence that our bogus medical device was actually safe for implantation into a human body.²⁰ He also said that IRB 3's board voted unanimously to reject our bogus protocol. Figure 3, below, shows additional examples of IRB 2's and IRB 3's comments on our fictitious medical device and protocol.

Figure 3: Examples of Statements by IRB 2 and IRB 3 Regarding Our Bogus Medical Device and Protocol



Source: GAO.

None of the three IRBs questioned us about the authenticity of our bogus CV and counterfeit medical license. As mentioned above, we fabricated these documents by using information found online and with commercially available hardware, software, and materials. Our bogus CV contained information on our fictitious researcher's human subjects research background, which we created by using phony drug and device names and with information that we accessed on the Internet. Our counterfeit medical license contained a bogus license number with a similar format to real license numbers used by the state we claimed our license was from.

¹⁹Sepsis is a life-threatening illness caused by a human immune system's overreaction to bacterial infection, which may lead to organ failure and death.

²⁰We did not verify the accuracy of the claims from IRB 2 and IRB 3 about the health risk posed by our fictitious medical device.

Briefing with HHS

We briefed HHS officials on the results of our investigation. They stated that HHS receives around 300 IRB registrations and 300 assurance applications every month, and that OHRP currently has three employees who review all registrations and applications. According to HHS officials, the department does not review IRB registrations or assurance applications to assess whether the information submitted is factual. HHS officials said that the department reviews assurance applications to ensure that applicants have submitted all of the necessary information and meet minimum standards. Moreover, although HHS is required by law to consider the adequacy of IRBs listed on assurance applications when reviewing applications,²¹ the director of OHRP stated that his office would require more staff to do so. However, HHS officials added that they would not consider additional evaluation of IRB registrations or assurance applications to be worthwhile even if the office had increased resources.

HHS officials stated that the assurance process is not a meaningful protection against unethical manipulation. They stated their belief that anyone submitting false or misleading information as part of the assurance application process would likely be detected during the subsequent process of applying for federal funding for human subjects research. However, our work shows that an unethical company could leverage an HHS assurance for purposes unrelated to the federal funding application process. For example, representatives from one of the IRBs that rejected our protocol stated that the HHS assurance number listed on our bogus medical device company's Web site gave our company credibility because it meant that HHS had recognized our company. When we discussed this with HHS, the director of OHRP acknowledged that an HHS-approved assurance is meaningful in this regard.

Mr. Chairman, this concludes our statement. We would be pleased to answer any questions that you or other members of the subcommittee may have at this time.

²¹45 C.F.R. § 46.103(d).

**Contacts and
Acknowledgments**

For further information about this testimony, please contact Gregory D. Kutz at (202) 512-6722 or kutzg@gao.gov. Contacts points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. GAO staff who made major contributions to this testimony include Matthew D. Harris, Assistant Director; Matthew Valenta, Assistant Director; Timothy Persons, Chief Scientist; Christopher W. Backley; Ryan Geach; Ken Hill; Jason Kelly; Barbara Lewis; Andrew McIntosh; Sandra Moore; James Murphy; and Seong B. Park.

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Mr. STUPAK. Thank you, Mr. Kutz. Dr. Less, your opening statement, please. And for all the witnesses if you have a longer statement than 5 minutes, it will be included in the record.

TESTIMONY OF JOANNE LESS

Ms. LESS. Good morning, Mr. Chairman, and members of the subcommittee. I am Joanne Less of the Good Clinical Practice Program at the FDA. I appreciate your invitation to appear here today to discuss FDA's role in overseeing Institutional Review Boards. For over 40 years, FDA has been committed to protecting the rights, safety, and welfare of subjects who participate in clinical trials of FDA-regulated products. The obligation to protect individuals who volunteer for research and assume research risks in order to advance public health and bio-medical knowledge is integral to FDA's mission, and the agency continually strives to strengthen and promote the human subject protections. While measures to protect subjects are incorporated into all aspects and all stages of clinical trial, perhaps human subject protection is most clearly embodied in 2 critical activities.

The first is the requirement to obtain voluntary, legally effective informed consent from each study subject. The second is a requirement for independent ethical review of each clinical trial. The responsibility for human subject protection is one that FDA shares with sponsors, clinical investigators, study monitors, and IRBs. Every party with a role in the conduct and management of the trial has clearly defined responsibilities under FDA's regulations. All of these parties must fulfill those duties and be vigilant in doing so or subjects could be put at risk. This network of overlapping responsibility is key to protecting the rights, safety, and welfare of subjects who participate in FDA-regulated trials.

IRBs are a critically important component of this collaborative oversight system. The primary purpose of IRB review is to assure the protection of the rights, safety, and welfare of human subjects. An IRB has the authority to approve, require modifications in or disapprove research. To approve a study, the IRB must determine that all of the following criteria are met. The risk to subjects are minimized, the risks are reasonable in relationship to anticipated benefits, selection of subjects is equitable, and informed consent will be obtained and documented. The IRB may require modifications to the protocol, informed consent or study procedures before it approves the study.

An IRB may disapprove a study due to protocol deficiencies or for reasons such as limited availability of suitable subjects. Once a study begins, IRBs are responsible for reviewing changes to research. IRBs have the authority to suspend or terminate approval of research that has been associated with unexpected serious harm to subjects. There are different types of IRBs. Most IRBs are established and operated by universities, hospitals, and other institutions. These IRBs are comprised primarily of volunteers from the institution's faculty and staff. A small number of IRBs, often referred to as independent IRBs, are not affiliated with such an institution.

Independent IRBs may provide reviews for industry-sponsored projects conducted outside a university or hospital, for example, in

a doctor's office. FDA applies the same oversight, scrutiny, and inspectional practices to all types of IRBs. The agency places a higher priority on inspecting IRBs that are new that have not been previously inspected, that have previously been found to be out of compliance or that are reviewing research involving high risk products or vulnerable populations. During these inspections, FDA investigators select one or more studies in the IRBs inventory. The inspector reviews the IRB procedures and records, follows the selected studies through the entire process, and interviews key staff.

FDA also conducts for-cause inspections of IRBs for which there have been complaints. During a for-cause inspection, FDA focuses on the issue identified in the complaint and determines if there is evidence to substantiate it. If an FDA investigator uncovers a regulatory violation, the agency may take further action. For minor deviations, FDA generally issues a letter describing the deficiency and provides reference to the relevant regulations or guidance. For more serious violations, FDA may issue a warning letter requesting that the IRB submit a corrective action plan within 15 days.

FDA generally conducts a follow-up inspection to ensure that the violations were corrected. The agency may also impose administrative sanctions on an IRB. For example, FDA may withhold approval of studies that are reviewed by the IRB, direct that no new subjects be enrolled in ongoing studies, or terminate all ongoing studies. Because the clinical trials process has significantly evolved since FDA issued some of its regulations, FDA launched an initiative aimed at modernizing and strengthening the agency's oversight of clinical trials. FDA issued a number of guidances with the expectation that they will reduce burdens, improve IRBs efficiency, and allow IRBs to give more attention to critical human subject protection activities.

Earlier this year, FDA issued regulations that would require all IRBs to register through an electronic system. This will enable the agency to more precisely identify IRBs that review FDA regulated research, assist us in providing educational information, and help us to identify IRBs for inspection. DA has also established a task force to ensure that all pending and future recommendations related to the agency's oversight of clinical trials raised by Congress, the HHS Office of the Inspector General, and the General Accountability Office are fully addressed.

Finally, although FDA has traditionally conducted a majority of its inspections in association with the submission of a marketing application, the agency has been shifting more of its resources to inspections of ongoing studies. This will allow the agency to identify potential problems while the study is still active enabling implementation of corrective actions to minimize risk to subjects and preserve the integrity of the trial. FDA has also been improving its follow-up of violative inspections and working to identify alternative methods to select IRBs for inspection. It is FDA's strong belief that educating IRB members, chairs, and administrators fosters understanding of the human subject protection regulations and enhances their ability to protect subjects participating in research.

To that end, in partnership with OHRP and other organizations, FDA participates in numerous national and regional conferences and workshops. In conclusion, FDA remains committed to strength-

ening human subject protection and improving its oversight of IRBs and other parties that conduct, oversee, and manage clinical trials. FDA has taken steps to ensure that recommendations regarding the agency's oversight of clinical trials, including IRBs, are fully addressed. While FDA has already implemented a number of changes to its clinical trial oversight activities, the agency continues to look for and welcome input about new approaches to fulfill these responsibilities. This concludes my statement. I would be happy to answer any questions.

[The prepared statement of Ms. Less follows:]

	<p>Statement Before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce United States House of Representatives</p>
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The Role of the Food and Drug Administration in Overseeing Subjects Participating in Clinical Trials

Statement of
Joanne R. Less, Ph.D.
Director
Good Clinical Practice Program
Office of the Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services



For Release on Delivery

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Joanne Less, Director of the Good Clinical Practice Program in the Office of the Commissioner, Food and Drug Administration (FDA or the Agency), an agency of the Department of Health and Human Services (HHS). I appreciate your invitation to appear here today to discuss FDA's role in overseeing Institutional Review Boards, commonly referred to as "IRBs."

BACKGROUND

For over 40 years, FDA has been committed to protecting the rights, safety, and welfare of subjects who participate in clinical trials of FDA-regulated products. The obligation to protect individuals who volunteer for research, and assume research risks in order to advance public health, therapeutics, and biomedical knowledge, is integral to FDA's mission, and the Agency continually strives to strengthen and promote the human subject protections embodied in our statute and regulations. While measures to protect human subjects are incorporated into all aspects and stages of a clinical investigation, perhaps human subject protection is most clearly embodied in two critical trial activities. The first is the requirement to obtain voluntary, legally effective informed consent from each study subject. The second, which is also the topic of this hearing, is the requirement for independent, ethical review of each clinical trial. Since 1962, with the passage of the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), clinical investigators have been required to obtain the informed consent of

subjects who participate in FDA-regulated research. IRB review has been a requirement for studies involving medical devices since 1976 with the enactment of the Medical Device Amendments and, by regulation, for all FDA-regulated research studies, since 1981.

However, regulators cannot ensure human subject protection by themselves. The responsibility for human subject protection is one that we share with sponsors, clinical investigators, study monitors, and IRBs. Some studies also include a data monitoring committee, which is an independent group of experts who monitor patient safety and treatment response data. Indeed, every party with a role in the conduct or management of the trial must fulfill those duties and be vigilant in doing so, or subjects could be put at risk.

As I mentioned before, responsibility for protecting the rights, safety, and welfare of human subjects who participate in biomedical research is shared by the sponsor, who is responsible for the overall conduct of the study; the clinical investigator, who conducts the study; the monitor, who verifies information submitted to the sponsor while the study is ongoing; the IRB, which is responsible for ensuring that the research is ethical and that the rights, safety, and welfare of the subjects are protected; and FDA, which has oversight responsibilities for the entire process. As described in more detail below, this network of overlapping responsibilities is key to protecting the rights, safety, and welfare of human subjects who participate in FDA-regulated trials.

OVERSIGHT OF CLINICAL TRIALS

Clinical trials are a means of testing investigational products in human volunteers to see if they should be approved for wider use in the general population. A test article could be a drug, medical device, or biologic, such as a vaccine or blood product. Test articles are generally studied in laboratory animals or subjected to other types of preclinical testing, such as *in vitro* bench or mechanical testing, before human trials are allowed to proceed. Investigational products having acceptable safety profiles are then moved into clinical trials.

The sponsor of a product to be studied develops an investigational plan, which includes the preclinical supporting data, the scientific justification for the study, a thorough description of the study interventions, plans for monitoring the study, and the informed consent process. The sponsor then selects one or more clinical investigators, appropriately qualified by training and experience, to conduct the trial and evaluate the test article.

In conducting clinical investigations of FDA-regulated products, the investigator is responsible for following the investigational plan and complying with all applicable regulations. Specific responsibilities related to protecting the rights, safety, and welfare of subjects under the investigator's care include, for example, complying with FDA's regulatory requirements for the initial and continuing review and approval of the proposed clinical study, obtaining the voluntary and legally effective informed consent of

each study subject, and promptly reporting any changes in the research activity to the IRB and sponsor prior to implementing them, except where necessary to eliminate apparent immediate hazards to the subjects.

FDA's regulations also require sponsors to monitor their investigations in order to ensure that the study is indeed being conducted according to the investigational plan and study protocol. During the trial, the study monitor may visit the investigational sites or use central monitoring techniques to assess the study's progress. The monitor will review records and case report forms to determine if the investigator is, among other things, accurately reporting adverse events. The monitor will also review the subjects' case histories to verify that the investigator is following the protocol's criteria for including subjects who qualify for the study, and excluding subjects whose medical condition or other factors (e.g., liver or kidney function, concomitant use of other medications) would place them at greater risk of harm if they were allowed to participate in the trial. Instances of noncompliance would be reported to the study sponsor, who must either secure the investigator's compliance or discontinue shipments of the investigational article and terminate the investigator's participation in the study.

I will now describe the responsibilities of the IRB.

WHAT IS AN INSTITUTIONAL REVIEW BOARD?

Under FDA regulations, an Institutional Review Board is a committee that has been formally designated to review, approve, and conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to ensure the protection of the rights and welfare of human subjects participating in the research. To accomplish this purpose, the IRB reviews research protocols, informed consent documents, and other materials (e.g., Investigator's Brochure, recruitment plans, advertising), and decides if the study should proceed.

In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. But in order to approve a study, the IRB must determine, among other things, that all of the following criteria are met: the risks to subjects are minimized; the risks are reasonable in relation to anticipated benefits; the selection of subjects is equitable; and informed consent is obtained and appropriately documented for each subject. So, for example, the IRB can require modifications to the protocol, informed consent document, or study procedures before it approves the study. And, as I mentioned earlier, under FDA regulations, the IRB also has the authority to disapprove a study. It should be noted that, in addition to protocol deficiencies, a study may be disapproved by an IRB for reasons beyond the protocol itself, such as current workload at the site or limited availability of suitable subjects.

FDA's regulations cover all aspects of an IRB's operations, including membership; procedures for initial, continuing, and expedited review; recordkeeping; and reporting requirements. For example, an IRB must have at least five members of varying backgrounds, including at least one nonscientist, and one nonaffiliated member as well as members who are sufficiently qualified through experience and expertise to review proposed research. An IRB may invite individuals with specialized knowledge to assist in the review of complex issues that require expertise beyond, or in addition to, that available on the IRB. In addition, when ensuring that the IRB is sufficiently qualified to review the research, consideration is also given to race, gender, cultural backgrounds, and sensitivity to the local community attitudes so as to promote respect for the advice and counsel of the IRB in safeguarding the rights and welfare of the subjects. IRB members may not participate in the IRB's review of, nor vote on, any project in which the member has a conflicting interest.

Once a study begins, IRBs have the authority to suspend or terminate approval of research that has been associated with unexpected serious harm to subjects or that is not being conducted in accordance with FDA's regulations or the IRB's requirements. Any suspension or termination of approval must include a statement of the reasons for the IRB's action and be reported promptly to the investigator, appropriate institutional officials, and FDA. Additionally, the IRB must follow its written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of any unanticipated problems involving risks to human subjects or others; any instance of serious or continuing noncompliance with these regulations or the requirements or

determinations of the IRB; or, as previously mentioned, any suspension or termination of IRB approval. IRBs do not operate in isolation, but rather, they act as part of a larger system intended to collectively ensure the protection of human subjects.

FDA JURISDICTION

FDA has authority over clinical trials involving products regulated by the Agency. This authority includes oversight of studies that are HHS-funded or supported (with joint oversight by FDA and the HHS Office for Human Research Protections (OHRP)), as well as studies that are funded by industry or private parties. FDA's regulations pertaining to IRBs and human subject protection are located at Title 21, *Code of Federal Regulations*, Parts 56 (21 CFR 56; "Institutional Review Boards") and 50: ("Protection of Human Subjects"). These regulations require that each IRB develop written procedures for conducting initial and continuing review of research, determining which studies require more frequent review, ensuring prompt reporting to the IRB of changes in research activity, and ensuring that changes in the research are not initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the human subjects. IRBs must also have, and follow, written procedures for promptly reporting to the IRB, FDA, and institutional officials any unanticipated problems involving risks to human subjects or others, any instance of serious or continuing noncompliance with FDA's regulations or the IRB's requirements, and any suspension or termination of the IRB's approval. These written procedures provide a framework for the

IRB's day-to-day operations and assist FDA's oversight of the IRB by providing a window into how the IRB functions.

There are different types of IRBs. Most IRBs are established and operated by universities, hospitals, and other institutions. While these institutions may receive research awards from the federal government, nonprofit foundations, or other sponsors, these institutionally based IRBs usually oversee all the clinical research conducted at their institutions, irrespective of the source of the funding for the research. These IRBs are comprised primarily of volunteers (i.e., faculty and staff members of the institution). A small number of IRBs, often referred to as "independent IRBs," are not affiliated with an institution. Independent IRBs usually provide reviews for industry sponsored projects conducted outside a university or hospital setting, e.g., in physicians' private offices or clinics. These IRBs also must comply with FDA's IRB regulations at 21 CFR Part 56. In other words, all IRBs that review FDA-regulated research, whether institutionally based or independent, are subject to the same regulatory requirements.

INSPECTIONS AND ENFORCEMENT

Each year, FDA's field staff conduct onsite inspections of Bioresearch Monitoring (BIMO) facilities, including sponsors, monitors, clinical investigators, IRBs, and laboratories that conduct nonclinical safety studies (including animal toxicity studies) to support FDA-regulated research. The Agency performs these inspections to evaluate the

inspected party's practices and procedures and to determine compliance with applicable regulations.

FDA applies the same oversight, scrutiny, and inspectional practices to independent IRBs as it does to IRBs that are linked to an academic or other institution. FDA conducts both surveillance and directed inspections of IRBs, and the Agency uses risk-based criteria to select these entities for surveillance inspections. For example, FDA places a higher priority on inspecting IRBs that are new or have not been previously inspected, IRBs that had previously been found to be out of compliance, and IRBs that are reviewing research involving high-risk products or vulnerable populations, such as pediatric subjects. During these inspections, FDA's inspectors will select one or more FDA-regulated studies in the IRB's inventory. The inspector will review the IRB's procedures and records, such as meeting minutes, membership rosters, progress reports, and correspondence with the clinical investigator. The inspector will follow the selected studies through the IRB's entire process, and interview key IRB staff. FDA's goal is to reconstruct the IRB's activities and ensure that the IRB's focus is on human subject protection, and that any controverted issues are resolved to the IRB's satisfaction. FDA also conducts directed (or "for-cause") inspections of IRBs for which complaints have been received. During a directed inspection, FDA focuses on the issues or study identified in the complaint and determines if there is evidence to substantiate the complaint.

If the FDA inspector uncovers a regulatory violation, the Agency may take further action. For minor deviations, FDA generally issues a letter describing the deficiency and provides reference to relevant regulations or guidance. For more serious violations, such as failure to ensure informed consent or failure to conduct continuing review of studies, FDA may issue a Warning Letter requesting that the IRB submit a corrective action plan within 15 days that describes how the IRB will correct the violations. FDA generally conducts follow-up inspections to ensure that the violations were corrected.

FDA may also impose administrative sanctions on an IRB found to be out of compliance with FDA's regulations. For example, FDA may withhold approval of studies that are reviewed by the IRBs, direct that no new subjects be enrolled in ongoing studies, or terminate ongoing studies, provided that doing so would not endanger study subjects. FDA may also impose specific restrictions, such as prohibiting the IRB from approving studies using expedited review procedures. FDA may also initiate disqualification proceedings against an IRB or its parent institution if the IRB has refused or repeatedly failed to comply with FDA's regulations and the noncompliance adversely affects the rights, safety, or welfare of the study subjects.

**FDA EFFORTS TO IMPROVE OVERSIGHT OF CLINICAL TRIALS -
HUMAN SUBJECT PROTECTION/BIORESEARCH MONITORING
(HSP/BIMO) INITIATIVE**

HSP/BIMO Initiative

In 2006, FDA launched the HSP/BIMO Initiative under the auspices of the Agency's Critical Path Initiative. The HSP/BIMO Initiative is aimed at modernizing and strengthening the Agency's oversight and protection of subjects in clinical trials and the integrity of resulting data.

For the past two years, the Agency has been working diligently to develop and issue new regulations and guidance to improve the conduct of clinical trials and enhance human subject protection. For example, FDA has long been aware that multiple individual adverse event (AE) reports were routinely submitted to IRBs, without any accompanying analysis or context as to their relevance to subject safety. As a consequence, IRBs have been struggling to manage the overwhelming volume of reports. To reduce this burden on IRBs and help provide for a more focused review, FDA issued guidance to assist sponsors and investigators in differentiating between AEs that are unanticipated problems that must be reported to an IRB and those that are not. In a similar vein, FDA has issued guidance on use of a centralized review process, data retention when a subject withdraws from a study, IRB review of Humanitarian Use Devices, and other topics, with the expectation that such guidance will reduce burdens, improve IRBs' efficiency, and allow IRBs to give more attention to critical human subject protection activities.

Earlier this year, FDA issued regulations that require all IRBs to register through an electronic system maintained by OHRP. Besides contact information for the IRB, the registration system includes the number of protocols involving FDA-regulated products reviewed during the preceding 12 months and a description of the types of FDA-regulated products involved in the protocols reviewed. These registration requirements will enable the Agency to more precisely identify IRBs that review FDA-regulated research, assist FDA in providing educational information to IRBs, and help us to identify IRBs for inspection.

Clinical Trial Transformation Initiative¹

Another effort to improve the quality of clinical trials and strengthen human subject protection is embodied in the Clinical Trial Transformation Initiative (CTTI). The result of a public-private partnership between FDA and Duke University, CTTI includes representatives from government, industry, patient advocacy groups, professional societies, and academia. CTTI's overarching goal is to identify practices which, if broadly adopted, are likely to increase the quality and efficiency of clinical trials. One of CTTI's first initiatives is a project to assess various clinical trial monitoring methods and thereby assist sponsors in selecting the most appropriate techniques for a specific trial. Other areas that CTTI may consider include exploring alternative models for IRBs in order to reduce

¹ www.trialstransformation.org

duplication of effort in multisite clinical trials and identifying strategies to enhance the informed consent process.

FDA Internal Task Force

FDA has also established a task force to ensure that all pending and future recommendations related to the Agency's oversight of clinical trials raised by Congress, the HHS Office of the Inspector General (OIG), and the Government Accountability Office (GAO) are fully addressed. For example, the OIG recommended that FDA establish procedures to enhance communication between its field and headquarters staff, develop criteria for initiating certain regulatory actions, and provide additional training to its staff in a number of areas. To address these recommendations, FDA recently added a section to the Compliance Program Guidance Manual (CPGM) chapter on Clinical Investigator Inspections that defines threshold criteria for issuing Warning Letters or notices initiating disqualification proceedings to clinical investigators, and includes instructions for determining if clinical investigators provided required financial disclosure information to trial sponsors.

In addition, FDA has developed and implemented internal procedures and guidance documents to provide direction to inspectional staff and to ensure consistency, transparency, and timeliness in FDA's process for disqualifying clinical investigators who repeatedly or deliberately fail to comply with regulations for human subject protection and the conduct of clinical investigations. Under Section 306 of the FD&C

Act, FDA has the authority to, among other actions, debar certain persons from the drug industry, such as companies and individuals convicted of crimes related to the drug approval process. FDA has finalized a guidance that consolidates the authority to initiate and pursue debarment actions within one Agency office. The new document also establishes specific procedures and timeframes for initiating, pursuing, and finalizing debarment actions.

Targeted Inspection Strategy

Finally, although FDA has traditionally conducted the majority of its BIMO inspections in association with the submission of a marketing application or as a part of its investigation of a complaint, the Agency has been focusing more on inspections of ongoing studies. This will allow the Agency to identify potential problems while a study is still active, enabling the implementation of corrective actions to minimize risks to human subjects and to preserve the integrity of the clinical trial. FDA has also been improving its follow-up of violative inspections and working to identify alternative methods to select IRBs for inspection. From information gleaned during clinical investigator and sponsor inspections, FDA works to identify potential problems with IRB operations and communications that might signal the need for an IRB inspection. This oversight includes investigations and enforcement if noncompliance with regulations in the operation of an IRB is apparent.

EDUCATIONAL ACTIVITIES

It is FDA's strong belief that educating IRB members, chairs, and administrators fosters understanding of the human subject protection regulations and enhances their ability to assure that the rights and welfare of human subjects participating in research are protected. To that end, in partnership with OHRP and other organizations, FDA participates in numerous national and regional educational conferences and workshops on human subject protection, research ethics, and good clinical practice. FDA continues to issue guidance on these issues, and responds to over 1,500 questions each year received from sponsors, investigators, and IRBs in an e-mail account dedicated to this purpose.

CONCLUSION

In conclusion, FDA remains committed to strengthening human subject protection and improving its oversight of IRBs and other parties who conduct, oversee, or manage clinical trials. FDA has taken steps to ensure that recommendations regarding the Agency's oversight of clinical trials, including IRBs, are fully addressed. While FDA has already implemented a number of changes to its clinical trial oversight activities, the Agency continues to look for and welcome input about new approaches and opportunities to fulfill these responsibilities. This concludes my statement and I would be happy to address any questions.

Please visit the Agency's Web site at http://www.fda.gov/oc/gcp/hsp_bimo.html to view FDA's HSP/BIMO Initiative Accomplishments Update

Mr. STUPAK. Thank you. Dr. Menikoff, your opening statement, please, sir.

TESTIMONY OF JERRY MENIKOFF, M.D.

Dr. MENIKOFF. Good morning, Mr. Chairman, and members of the subcommittee. I am Jerry Menikoff, Director of the Office for Human Research Protections which is within the Department of Health and Human Services. I previously served as director of the office that oversees the NIH's human research protection program. Before that, for almost a decade, I chaired the Institutional Review Board at the University of Kansas Medical Center. The department's commitment to human subject protections spans more than 3 decades. In 1974 what was then known as the Department of HEW issued its first department-wide human subject protection regulations. OHRP is charged with enforcing the current regulations which are in 45 CFR part 46.

OHRP's mission is to protect the rights, welfare, and well-being of subjects involved in research conducted or supported by the department. The responsibility for protecting research subjects is one that OHRP shares with the FDA, agencies that fund research, institutions that conduct research, investigators who carry out that research, and the IRBs that review it. Everyone with a role in human subjects research must fulfill their duty to protect the subjects or else those subjects could be at undue risk. The core provisions of the department's current human subjects regulations cover three major areas. First, institutions conducting HHS funded research must enter into an agreement called an assurance agreeing to comply with the regulations. Second, a committee called an Institutional Review Board or IRB must review and approve the research before enrollment of any subject. The IRB plays a central role in ensuring that the rights, safety, and welfare of subjects are adequately protected.

Third, the research must be conducted consistent with the regulations, which generally require obtaining the informed consent of the subjects and the IRB's continuing review of the research. The department's regulation in addition provides special protections for various populations considered to be vulnerable. Besides the regulations administered by OHRP, there are other federal regulations protecting research subjects. The FDA has its own set of regulations. These apply to clinical trials involving products regulated by FDA. These regulations are substantially similar to those administered by OHRP, though there are some differences.

In 1991, 14 other federal departments and agencies joined HHS in adopting a uniform set of regulations that are identical to the core portion of the HHS regulations. This set of regulations is often referred to as the common rule. For all participating federal department and agencies the common rule outlines the same basic provisions for IRBs informed consent and assurance agreements. As I noted, the department's regulations require that institutions that are engaged in HHS funded research must sign an agreement with OHRP known as an assurance. Through this assurance the institution commits itself to have all its HHS-funded research conducted in compliance with the regulations.

Assurances must also include designation of one or more IRBs that will review the research covered by the assurance. The institution holds primary responsibility for ensuring that the IRBs it designates are appropriately qualified to review the types of research studies it conducts. The Federalwide Assurance, or FWA, was introduced in 2000 and has been the only type of assurance accepted by OHRP since 2005. Previously, OHRP reviewed assurances using procedures that often involved lengthy discussions with institutions. In 1998, the HHS Office of Inspector General recommended that OHRP shift its focus and resources to other parts of the system so as to better protect research subjects. The current largely automated system for processing FWAs was implemented as a response to that OIG report.

With the adoption of the FWA system in 2000, a new requirement was added. Any IRB designated under an FWA must be registered with OHRP. The process for registering an IRB with OHRP is separate from the process for obtaining FWA but the two are related. This registration process was implemented in response to a recommendation from that same OIG report. The report recommended a simple registration system which would collect minimal descriptive information such as location and contact information. This simplified registration system would still allow OHRP and FDA to communicate effectively with IRBs while maintaining the standards of protection for research subjects.

The IRB registration process requires among other things submission of a list of IRB members identified by name, qualification, and affiliations. OHRP generally accepts all IRB registration applications that include information showing compliance with the following requirements, that there are at least five IRB members, there is at least one person designated as a non-scientist and one designated as a scientist, and then there is at least one member designated as not affiliated with the institution. On January 15 of this year both OHRP and FDA issued IRB registration rules. The two sets of registration rules are quite harmonious and will be implemented through a single web-based IRB registration system.

In conclusion, the protection of research subjects remains a highest priority for both the department and for OHRP. We continue to work on ways to better achieve that goal and very much welcome any recommendations that the subcommittee may have. Thank you for this opportunity to address you. I will be pleased to answer any questions.

[The prepared statement of Dr. Menikoff follows:]



Testimony
Before the Subcommittee on Oversight and
Investigations
Committee on Energy and Commerce
United States House of Representatives

**The Role of the HHS Office for Human
Research Protections in Protecting
Human Research Subjects**

Statement of

Jerry A. Menikoff, M.D., J.D.

Director

Office for Human Research Protections

Office of Public Health and Science

U.S. Department of Health and Human Services



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Good morning, Mr. Chairman and members of the Subcommittee. I am Jerry Menikoff, Director of the Office for Human Research Protections (OHRP) within the Office of Public Health and Science, Department of Health and Human Services (HHS). I previously served as the director of the office that oversees the human research protection program at the National Institutes of Health (NIH), and as a bioethicist in the NIH Clinical Center's Department of Bioethics. Before that, for almost a decade I was on the faculty of the University of Kansas and chaired the Institutional Review Board (IRB) at the University of Kansas Medical Center. I have also been a faculty fellow in bioethics at Harvard University and at the University of Chicago. I am pleased to appear before you to discuss the HHS regulations for protection of human subjects, particularly as they relate to OHRP's assurance and IRB registration processes.

OHRP is the component within HHS that is charged with enforcing the Department's protection of human subjects regulations at 45 CFR part 46. OHRP protects the rights, welfare, and well-being of subjects involved in research conducted or supported by HHS by working to ensure that such research is carried out in accordance with those regulations. The codification of human subject protections spans over three decades. On May 30, 1974, the then-Department of Health, Education, and Welfare issued the first Department-wide human subjects protection regulations.

The responsibility for human subject protections is one that OHRP, as a regulator, shares with the Food and Drug Administration (FDA), the HHS agencies that fund research, the research institutions that obtain HHS funds to conduct research, the investigators who carry out HHS-

funded research, and the IRBs that review HHS-funded research. All persons and entities with a role in the conduct or management of human subjects research must fulfill their duty to protect human subjects or subjects could be put at undue risk.

Background

The core provisions of the HHS protection of human subjects regulations are found in subpart A of 45 CFR part 46, referred to as the Basic HHS Policy for Protection of Human Research Subjects, and can be divided into three major areas:

- Requirements regarding submission of a written agreement by an institution conducting HHS-funded non-exempt human subjects research that it will comply with all requirements of the regulations. These agreements are called “assurance” agreements;
- Requirements regarding the review of research, before any subject can be enrolled in a research study, by an IRB; and
- Requirements regarding the actual conduct of the research, including obtaining and documenting of the informed consent of human subjects involved in research, and continuing review by the IRB.

By providing independent ethical review of research, the IRB plays a central role in ensuring that the rights, safety, and welfare of human subjects are adequately protected. The HHS protection of human subjects regulations require IRBs to possess the professional competence necessary to

review specific research activities, and to be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must also be sufficiently qualified through the experience, expertise, and diversity of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

Before an IRB may approve research under the HHS regulations, it must have sufficient expertise and information to ensure, among other things, that risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, and that selection of subjects is equitable. Knowledge about the research institution and the qualifications of the investigators that will carry out the research are important considerations in the IRB's assessment.

The IRB also must ensure that the research includes adequate provision for obtaining and documenting the informed consent of the subjects, except in limited circumstances where the IRB may waive these requirements. These informed consent provisions are designed to allow potential subjects to be made fully aware of the following, among other things:

- The purpose of the research, the expected duration of the subject's participation, the procedures to be followed in the research, and identification of any procedures that are experimental;
- Any reasonably foreseeable risks or discomforts;
- Any reasonably expected benefits to the subjects or to others;

- Appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subjects.

Over the years, HHS has adopted additional research protections for various populations considered to be particularly vulnerable. These are in addition to the basic protections for human subjects in subpart A. The additional protections include:

- Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (codified at Subpart B of the regulations);
- Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (codified at Subpart C); and
- Protections for Children Involved as Subjects in Research (codified at Subpart D).

Additional Human Subject Protection Regulations

There are additional federal regulations relating to the protection of research subjects beyond those which are administered by OHRP. In particular within HHS, the FDA has its own set of regulations that apply to clinical trials involving products regulated by FDA. These regulations are substantially similar to 45 CFR part 46 with respect to IRB review, informed consent, and the protections for children involved as subjects in research, but they differ some other respects.

In 1991, fourteen other Federal departments and agencies joined HHS in adopting a uniform set of regulations that are identical to subpart A of 45 CFR part 46. This uniform set of regulations

is known as the Federal Policy for the Protection of Human Subjects, also referred to as the “Common Rule.” Two other federal entities, the Central Intelligence Agency and the Department of Homeland Security, must comply with all parts of 45 CFR part 46. For all participating Federal departments and agencies the Common Rule outlines the basic provisions for IRBs, informed consent, and assurances of compliance.

Organization of OHRP

OHRP provides leadership in the protection of human subjects participating in research conducted or supported by HHS by providing clarification and guidance, developing educational programs and materials, and maintaining regulatory oversight. OHRP is organized into three functional Divisions: Compliance Oversight, Education and Development, and Policy and Assurances. In addition, there is the Office of the Director.

OHRP’s Division of Compliance Oversight evaluates written substantive indications of noncompliance with the HHS protection of human subjects regulations. OHRP typically asks the institution involved to investigate the allegations and to provide OHRP with a written report of its investigation. OHRP then determines what, if any, regulatory action needs to be taken to protect human research subjects. OHRP’s compliance oversight determination letters are posted on its website.¹ OHRP also conducts on-site evaluations at research institutions, in response to indications of possible serious noncompliance. In addition, OHRP conducts not-for-cause

¹ <http://www.hhs.gov/ohrp>

evaluations of institutions.

The Division of Education and Development provides guidance to individuals and institutions conducting HHS-supported human subject research; conducts national and regional conferences; participates in professional, academic, and association conferences; and develops and distributes resource materials in an effort to improve protections for human research subjects. The Division also helps institutions assess and improve their human research protection programs through quality improvement consultations.

The Division of Policy and Assurances prepares policies and guidance documents and interpretations of requirements for human subject protections and disseminates this information to the research community. The Division also administers the assurances of compliance and implements the IRB registration process.

Within the Office of the Director, OHRP has established an International Program that provides training to institutions involved in international research to help ensure that ethical protections are afforded to those who participate in research outside the United States, as well as quality improvement assurance consultations to international institutions. In addition, OHRP provides technical and logistical support to the Secretary's Advisory Committee on Human Research Protections (SACHRP), and OHRP's director serves as the Executive Secretary to SACHRP. SACHRP advises the HHS Secretary on issues of human subject protections. The OHRP director also co-chairs the interagency Human Subjects Research Subcommittee whose

membership includes representatives of all the Common Rule agencies, and which reports to the Committee on Science of the National Science and Technology Council (NSTC). Chaired by the President, NSTC is a Cabinet-level Council that serves as the principal means within the executive branch to coordinate science and technology policy across diverse entities that make up the Federal research and development enterprise.

The Assurance Process

The regulations at 45 CFR part 46 require institutions that are engaged in human subjects research conducted or supported by HHS to file with OHRP an assurance of compliance with the HHS human subjects protection regulations. In particular, the institution is agreeing that all research that is funded by the Department will be conducted in compliance with certain ethical principles and in compliance with the HHS protection of human subjects regulations. In addition, through its assurance, a domestic institution may voluntarily commit to extend these protections to all its human subjects research, regardless of funding source. Many institutions choose to do so.

The assurance must be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the HHS protection of human subjects regulations. Assurances for HHS-conducted or –supported research must include designation of one or more IRBs that will review the research covered by the assurance.

The institution that is seeking an assurance or already holds an assurance has a responsibility to ensure that the IRBs designated in its assurance are appropriately constituted to review and approve human subjects research covered by the institution's assurance. The institution submitting or holding an assurance is best positioned to assess whether the IRBs it designates possess the competence and expertise necessary to review the research that the institution expects to conduct.

The Federalwide Assurance (FWA) was introduced in 2000 and has been the only type of assurance accepted by OHRP since 2005. Prior to 2005, OHRP and its predecessor, the Office for Protection from Research Risks (OPRR), accepted several types of assurances, including general assurances, cooperative project assurances, multiple project assurances, and single project assurances. The procedures relating to the creation of these documents often involved lengthy discussions with institutions. In 1998, the HHS Office of Inspector General issued a report, *Institutional Review Boards: A Time for Reform*, concluding that this process for obtaining an assurance could be improved. The current largely automated system for processing FWAs was implemented as a response to that OIG Report.

OHRP approves FWAs for federalwide use, which means that other Federal departments or agencies that have adopted the Common Rule may rely on the FWA for research that they conduct or support. Most of these Federal entities accept the FWA, although a few approve their own assurances for some of the research that they conduct or support.

The FWA system, consistent with the OIG recommendations, provides a simplified assurance process that replaces the prior assurance mechanisms used by OHRP, which were more complicated and burdensome than the FWA. Institutions submitting a new FWA may submit all information for initial FWAs, or updates and renewals of existing FWAs via the internet using an interactive page on the OHRP website, with the signature of the Signatory Official submitted on via mail or facsimile.

OHRP generally approves all FWA applications that include the required information that is collected on the OMB-approved FWA form (OMB No. 0990-0278). Required information includes the legal name and location of the institution filing the FWA; a list of components over which the institution submitting the FWA has legal authority that operate under a different name and any alternate name under which the institution operates; a list of the IRBs, by name and registration number, that are to be designated under the FWA; and the names of, and contact information for, the human protection administrator (the person who can serve as primary point of contact for the institution's system for protecting human subjects) and the signatory official (the institutional official legally authorized to represent the institution). The signatory official must sign the FWA and has the responsibility to assure that human subjects research to which the FWA applies is conducted in accordance with the terms of the agreement.

With the adoption of the FWA system in 2000, OHRP's process for reviewing FWAs has been

streamlined and simplified, resulting in a significant reduction in administrative burdens both for institutions submitting assurances to OHRP and for OHRP. Submission of an IRB membership list has always been a component of every type of assurance approved by OPRR and OHRP, as well as assurances approved by other federal departments and agencies that adopted the Common Rule. However, one prerequisite that was implemented by OHRP with adoption of the FWA in 2000 is that any IRB designated under an FWA first must be registered with OHRP. The process for registering an IRB with OHRP is separate from the process of obtaining an OHRP-approved FWA. The IRB registration process includes submission of an IRB membership list.

Currently there are more than 10,000 OHRP-approved FWAs; of these, 76 percent are FWAs for U.S. institutions and 24 percent are FWAs for international institutions.

IRB Registration Process

The OHRP IRB registration process was first developed in 2000 in response to another recommendation from the 1998 OIG Report. In recommending this new system, the OIG was specifically concerned about the possibility that it might become an inappropriate burden to the research process. The Report accordingly made it clear that all that was needed was “a simple registration system in which IRBs regularly update the Federal government on minimal descriptive information” such as location and contact information. The registration system would, among other things, enable OHRP and the FDA to communicate more effectively with

IRBs and thus provide improved protections to human research subjects.

The IRB registration process was also designed to collect information required under the HHS human subjects protection regulations at 45 CFR 46.103, including a list of IRB members (IRB roster) identified by name, qualifications, and affiliations. The IRB registration process was also designed to collect additional information to be provided voluntarily by institutions or IRBs regarding the accreditation status of the institution or IRB organization, total numbers of active research protocols reviewed by the IRB (including protocols supported by other Federal departments or agencies) and the nature of those protocols, and IRB staffing.

Recently, on January 15, 2009, OHRP issued a new IRB registration final rule that will require submission of some of the information that was being submitted voluntarily (e.g., approximate number of all active protocols and those conducted or supported by HHS, and the approximate number of full time equivalent positions). FDA also issued an IRB registration final rule on January 15, 2009 that creates new requirements for IRBs in the U.S. that review clinical investigations that are regulated by FDA. OHRP's and FDA's IRB registration rules are compatible and largely harmonious, and will be implemented through a single registration system that will be accessible through the OHRP website. That web-based IRB registration system is being designed to be largely automated, so that little staff time will be required for the acceptance of IRB registration applications.

Organizations registering new IRBs or updating or renewing already registered IRBs may submit all information via the internet using an interactive page on the OHRP website. Beginning on July 14, 2009, the effective date of OHRP's IRB registration rule, each IRB that is covered by the HHS regulations for the protection of human subjects must be registered electronically, unless an institution or organization lacks the ability to register its IRB(s) electronically. In such a case, the organization must send its IRB registration information in writing to OHRP.

OHRP generally accepts all IRB registration applications that include the required registration information that is collected on the OMB-approved IRB Registration form (OMB No. 0990-0279). Required information includes: the name and mailing address of the institution operating the IRB; name of, and contact information for, the institution's or organization's head official; each IRB chairperson's name and contact information; and the IRB roster that includes, for each member, their name, gender, degree, a designation of whether their area of concern is in a scientific or nonscientific area, and a designation of whether they are affiliated or not affiliated with the institution that is registering the IRB.

When reviewing an IRB membership list in the context of IRB registration, OHRP ascertains that the IRB satisfies the following minimum requirements of the HHS regulations on protection of human subjects at 45 CFR 46.107:

- there are at least five members listed;
- at least one member is designated as having primary concerns in scientific areas;

- at least one member is designated as having primary concerns in nonscientific areas; and
- at least one member is designating as being not otherwise affiliated with the institution registering the IRB.

Currently there are more than 6,000 IRBs registered with OHRP. Of that number, 60 percent are IRBs that are located in the U.S. and 40 percent are IRBs that are located abroad.

OHRP makes information collected in the IRB Registration System and the FWA system available to other Federal departments and agencies that have adopted the Common Rule and that find that a FWA is appropriate for the human subjects research they conduct or support. The information enables these entities to confirm that a particular institution holds an applicable assurance approved for Federalwide use (i.e., that it has agreed to be bound by the applicable regulations) and identify an institution's designated IRB(s) before making an award to that institution to support research involving human subjects.

Conclusion

Through this system of assurances of compliance, IRB review, and informed consent, the HHS regulations are designed to protect the rights and welfare of human subjects, while enabling the conduct of important, ethical research. The protection of human subjects in research studies is a priority for the Department, and it is the mission of OHRP to support, strengthen and provide leadership to the nation's system for protecting research subjects who participate in research that is conducted or supported by HHS.

Thank you for this opportunity to present this information to you. I would be happy to answer any questions you may have.

Mr. STUPAK. Thank you, Dr. Menikoff. Mr. Dueber, your opening statement, please, sir.

TESTIMONY OF DANIEL DUEBER

Mr. DUEBER. Good morning. Coast IRB recently submitted the product in question, Adhesiabloc, to an independent forensic toxicological lab. That lab determined, as we did, as our board did on October 30, that the product was safe. Here is the conclusion by two top forensic toxicologists in the United States. It is my opinion within a reasonable degree of scientific certainty there is no sound scientific foundation for finding the constituents in the Adhesiabloc gel described in clinical study protocol pilot study of safety and efficacy of 2.5 percent Adhesiabloc gel to reduce adhesions following peritoneal cavity surgery, device clinical study protocol number P-D-15 version 1.4, unsafe at the dose recommended for testing.

In October of 2008, the Government Accountability Office, at the behest of this committee, perpetrated an extensive fraud against my company, Coast IRB, LLC. It did so without probable cause that Coast had committed any crime. Indeed, no one at Coast has committed any crime. It did so without involving the executive branch. It did so without satisfying any of the legal safeguards that the Department of Justice and the federal courts have in place. It acted without probable cause that a crime had been committed.

If this committee's objective with this fraudulent and illegal GAO sting operation was to demonstrate that IRBs need to do more checking and verification of sponsor and PI licenses, verify the existence of companies and so on, fine, we will do that. And we have changed our SOPs to do just that because of this illegal fraud. But did you have to take the extremely negative approach of setting up an elaborate, expensive fraud? Yes, your fraud was very sophisticated, and you pulled the wool over our eyes. Congratulations. But you need to understand the effects of this charade. I personally have wasted 5 weeks of my valuable time defending the honor, integrity, and reputation of both our company and of me. We have spent many years building that.

My company has now spent over \$100,000 defending itself, and do you know what that means? That means that we now have to lay off at least five people at our company to pay for this. A much better and positive approach would have been for you to call a conference together of key IRB industry leaders, FDA, OHRP, and the committee to identify what needs to be fixed and what laws, regulations are needed to fix the problem. No one would have had to have been harassed as Coast has with this sting. The GAO posed as a private business seeking review by my company of a medical device. It represented the medical device to be one that was substantially equivalent to a device approved for market by FDA.

In an elaborate scheme, GAO violated federal and state laws, one, by falsely representing itself to be a medical device company, two, by submitting a fake clinical trial address, three, by submitting a fraudulent protocol for a fraudulent medical device, four, by submitting a forged CV for a fake principal investigator, five, by falsely representing the medical device to be substantially equivalent to a device approved by FDA for market, six, by submitting a fraudulent FDA 510(k) number for the device, seven, by submitting

a fraudulent Federalwide Assurance number, and eight, by forging a Commonwealth of Virginia medical license and license numbers for its supposed principal investigator.

GAO also engaged in extensive verbal and e-mail correspondence with Coast IRB in furtherance of the fraud. The fraud would have persisted to this day had I not discovered it and had Coast not terminated the clinical trial. Had I not discovered it following receipt of this committee's request for documents, I am confident it would have been discovered before its next scheduled review of the trial in April, next month. Mr. Chairman, it is the exclusive duty and province of the executive branch of this government to engage in law enforcement actions. By well settled precedent that branch alone may engage in clandestine stings upon probable cause that a crime has been committed. Innocent citizens of this country cannot be lawfully defrauded by their government. To hold otherwise replaces the rule of law with tyranny.

Mr. Chairman, what the GAO has done at the request of this committee is unlawful. The actions here involve mail fraud, wire fraud, forging of a Commonwealth of Virginia medical license, false presentation of license numbers and 510(k) numbers, and false holding out of people to be physicians in the Commonwealth of Virginia. Coast has notified federal and state law enforcement of these crimes. These are crimes whether committed by the GAO or anyone else in the absence of probable cause. They are crimes for which those responsible should answer. Although we have informed law enforcement that GAO is behind them, a fact never affirmatively confirmed by your committee staff to me, we have asked that the crimes be investigated and that those responsible be prosecuted.

Mr. Chairman, the question confronting me, and which I hope will occur to you, is whether this committee and the GAO have the lawful authority to defraud an innocent party to prove a political point. My question, sir, is whether this committee and the GAO are above the law. You know, I am just very, very saddened and disappointed in our government right now. I cannot believe my government did this to me and my company. It is unconscionable. But Coast IRB shares everyone's concern in this room about the need to improve our oversight system. We have been at the forefront in the past about documenting the need for improvements in ICFs and IRB shopping and other categories. We want to work with FDA and this committee to improve the system in a positive way. Thank you, and I will be happy to answer any questions.

[The prepared statement of Mr. Dueber follows:]

OPENING STATEMENT
OF DANIEL S. DUEBER, CEO, COAST IRB, LLC

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It did so without involving the executive branch. It did so without satisfying any of the legal safeguards that the Department of Justice and the federal courts have in place. It acted without probable cause that a crime had been committed.

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Mr. Chairman, the question confronting me, and which I hope will occur to you, is whether this Committee and the GAO have the lawful authority to defraud an innocent party to prove a political point.

My question, Sir, is whether this Committee and the GAO are above the law.

Mr. STUPAK. The members will be recognized for 5 minutes for questions. I will begin. Mr. Dueber, I have to tell you how disappointed I am, I think Mr. Walden said the same thing, and the other members who are up here, with your opening statement. Coast IRB could have come forward this morning and admitted that they made numerous mistakes by not checking into the credentials of a fake company, a fake doctor, and a fake device that Coast ultimately approved for use in human testing. Instead, like a kid who has got caught with his hand in the cookie jar, you now come before Congress today to complain that you were caught. Nowhere in your opening statement is there any sense of concern that your company's approval could have led to human subjects being exposed to a dangerous substance without testing. Lives could have been injured or lost as a result of your company's action, and all you do is complain that you were caught.

Where is the first responsibility and where is the corporate responsibility? So let me ask you this, Mr. Dueber, you were interviewed on the record by committee staff last week. They asked you some basic questions about your medical review of GAO's experimental testing protocol. And let me put them on the screen. Here are your answers. When our counsel asked you, do you feel your company's medical review of the protocol was adequate, you indicated yes. So is it fair to say that none of the board members, including Dr. Dodd, who did the primary medical review, has raised concerns with the medical review of this protocol? Is that fair to say that you have no concerns about the protocol?

Mr. DUEBER. This was a sophisticated fraud, sir.

Mr. STUPAK. My question is, is it your opinion that the medical review was fair in this case?

Mr. DUEBER. We reviewed—we did a safety review. Dr. Dodd looked at the protocol.

Mr. STUPAK. And you feel it is safe?

Mr. DUEBER. We checked with—Dr. Dodd made the conviction—made the conclusion that it was safe, and we have just proven that it is safe with an independent review of—

Mr. STUPAK. Sure, your independent review, you talk about the 2.5 percent of the Adhesiabloc. What about the 97.5 percent of the liter that would be left in the woman's abdomen? What about that 97 percent? You don't even know that it is, so how can you test to see if it is even safe in your little report you have there from your expert?

Mr. DUEBER. He looked at it and he said that—

Mr. STUPAK. He looked at what? 2.5 percent, that is what he looked at.

Mr. DUEBER. He looked at the whole device.

Mr. STUPAK. Look at your protocol. You are going to leave 1 liter behind. What about the other 97.5 percent of the liter that you have no idea what it was in our protocol because you never asked.

Mr. DUEBER. Well, sir—

Mr. STUPAK. So, therefore, you can't sit here and say the other 97.5 percent has been tested and safe when you don't know what the tests were because you don't know what the product contains.

Mr. DUEBER. Sir, I am not a scientist. I did not do the primary—

Mr. STUPAK. Neither am I.

Mr. DUEBER. But what I can tell you is that Dr. Dodd told me when I talked to him about this that this propylene glycol substance—

Mr. STUPAK. Which is 2.5 percent, 1 liter, is safe. Didn't the doctor tell you what the other 97.5 percent was?

Mr. DUEBER. We didn't discuss—

Mr. STUPAK. You didn't ask? What if it is poison? So let me go on. GAO submitted this fake protocol to 2 other IRBs that came to exactly the opposite conclusion than you did. They both rejected the study. The first IRB that rejected the study was a company called Argus IRB. Here is what they said. We realized it was a terrible risk for the patient. The concept of the study was risky. It is the worse thing I have ever seen. Doing a surgery, a major surgery, on a patient, then a mystery guy walks in and dumps a solution in the body. Where is the safety for the patient? Who is overlooking all these parts? Who is looking for the patient—who is looking out for the patient? I had a problem with propylene glycol gel. They said it was a safe substance. I didn't see any data on it. There was no data in the protocol indicating that propylene glycol gel was safe internally. It was a serious problem.

Mr. Dueber, how is it possible that your company found that this study wasn't risky at all when other IRBs rejected it? And actually a second IRB called Fox Company, they said I could have sent the protocol to Board of Review but I spared wasting their time. There was no monitoring for safety. It appeared that people were just going to go out and start injecting people. Mr. Dueber, given what the other IRBs found, don't you think your company made a major mistake here?

Mr. DUEBER. Our company followed the regulations that FDA requires.

Mr. STUPAK. Really? Where is the due diligence in your company? Where is the safety of the patient by injecting them with a liter bottle and 97.5 percent—

Mr. DUEBER. It had a 510(k) exemption for one thing.

Mr. STUPAK. Did you go check that 510(k)?

Mr. DUEBER. No, we did not.

Mr. STUPAK. Is that part of due diligence, checking a 510(k)? You relied on it.

Mr. DUEBER. It is now. We have changed our SOPs to incorporate those since we have been now hoodwinked by our government.

Mr. STUPAK. My time is up. Mr. Kutz, let me ask you this last question, if I can. Do you believe Coast's medical review was adequate? Do you agree with Mr. Dueber that there was no risk involved with injecting a liter of this mystery substance into a woman's abdominal cavity?

Mr. KUTZ. I don't have the expertise to say that, but what I would say is this is if you have a system where two companies can say this thing is the riskiest thing they have ever seen and they rejected it even in some cases before it got to the board, and at the same time we have an IRB that says this is perfectly safe, we got a real problem here. So I think that would be what I can say based on my expertise.

Mr. STUPAK. Thank you. And I recognize Mr. Walden for 5 minutes, please.

Mr. WALDEN. Thank you, Mr. Chairman. Mr. Dueber, I want to go to this report from I guess it is Kupeck Group, LLC, because he says in my opinion within a reasonable degree of scientific certainty there is no sound scientific foundation for finding that constituents in the Adhesiabloc gel described in clinical study protocol pilot study, blah, blah, blah, are unsafe at the dose recommended for testing. Is that the same thing as saying the entire grouping of those items in this proposed gel are safe? Does his report actually say or this company's report actually say that the entire compilation and usage of the gel was safe or just that the two constituent ingredients alone are safe?

Mr. DUEBER. That is our understanding. We asked him to review the gel at the 2.5 percent for this study and for the amount left in the cavity and he said that it is not unsafe at this dose recommended for testing.

Mr. WALDEN. And so is he saying to you then that he would have approved it for use in human subjects?

Mr. DUEBER. That is the way we understood it, yes.

Mr. WALDEN. And left in their stomach, sir, their belly for up to 5 months?

Mr. DUEBER. Yes.

Mr. WALDEN. Where does it say that in the report? I don't see it in the conclusion, and where does it discuss the procedures involved?

Mr. DUEBER. I haven't had the opportunity to read the whole report.

Mr. WALDEN. When did you ask for the report, sir?

Mr. DUEBER. Several days ago.

Mr. WALDEN. So what report did you ask for that would have shown this was safe when your board approved this gel 70?

Mr. DUEBER. Well, as I—excuse me.

Mr. WALDEN. While you are consulting with counsel, I will go to Dr. Menikoff. You can continue to consult if you need to. Dr. Menikoff, obviously you are representing HHS. You heard my comments. I heard yours in terms of more of a recitation of what the rules and the procedures are for your agency and the same from Dr. Less for FDA. What troubles me greatly, and I think what troubles the people I represent, is that virtually anybody even with the most silly of applications can register as an IRB simply by emailing your agency and it gets entered even if the name of the town you are from is Chetesville, Arizona for which I assume there is no zip code. Is this preventable?

Dr. MENIKOFF. Congressman, it is true that anybody could enter information into the registration system. The registration system was a response to the very OIG report that several of you commented on, and it basically established the registration system, a method of collecting minimal information so there would be a list of IRBs.

Mr. WALDEN. What do you do with that information mostly?

Dr. MENIKOFF. We use it to contact IRBs to send information to them.

Mr. WALDEN. Information about that?

Dr. MENIKOFF. About a change in the system. There may be a compliance allegation alleged against a particular IRB, so we will contact them using the contact information.

Mr. WALDEN. Do you use it to contact them about conferences and things?

Dr. MENIKOFF. It could sometimes be used for that. Absolutely.

Mr. WALDEN. Mr. Dueber, let me go back to you because I sense you may have an answer to my question.

Mr. DUEBER. Yes, sir. The primary reviewer on this, Dr. Dodd—

Mr. WALDEN. Very distinguished credentials, by the way.

Mr. DUEBER. Yes. And he is very familiar with propylene glycol which is the basis of this substance, and he told me that propylene glycol can be ingested in large amounts in the body and is not toxic and that it is proven to be non-cancerous. There has been no question about its toxicity in any part of the body even remaining in the body for a period of time. He is an expert medical reviewer for the California Medical Board. He is chief of staff at the Lodi Medical Hospital. He is chairman of his Institutional Review Board at Lodi Medical Hospital. He is an OB/GYN also. He knows his stuff.

Mr. WALDEN. All right. I am sure he does. Dr. Less, since you are FDA, is there any problem with ingesting this chemical in your body and having it sit there for 5 months and in concert with the surgeries and all?

Ms. LESS. Having not—

Mr. WALDEN. You can't answer that?

Ms. LESS. I was just going to say having not seen the device description pre-clinical test and by compatibility testing, we wouldn't be able to comment on that.

Mr. WALDEN. Mr. Kutz, maybe you can help us here. What did the other IRBs say about this procedure and the protocols and the tests and all?

Mr. KUTZ. I think it is important to know that because it goes beyond just is the product safe. If could read a few of their comments to you, if that is OK.

Mr. WALDEN. Please.

Mr. KUTZ. The first one, as you mentioned, said that our submission was so bad they weren't even going to give it to the board. They also said that our protocol showed no evidence of quality control for sterility or consistency of the product. The next comment is very, very important. They said there was no prior investigation report of the pre-clinical animal studies we claimed to have performed, and they wanted to know whether there had been any adverse events, whether our product killed animals or hurt animals.

The second IRB said who is the manufacturer of Adhesiabloc and where is it made? It seems like a logical question. We didn't put that in our protocols. Where will these surgeries take place? That wasn't in our protocols. How are the hospitals and surgeons being selected? That wasn't noted. Has the surgeon or hospital read the protocols and do they agree? We didn't answer that. Provide the diagram used to record the incision lines. And the last one that seems fairly relevant when you are discussing it, who will be performing and taking the tissues and biopsies? So those are some of the substantive comments.

Mr. WALDEN. Mr. Kutz, did this IRB, which by the way made itself known to the public through their public relations outreach efforts, you didn't do that, did you?

Mr. KUTZ. No, we never used—

Mr. WALDEN. And we did not. And so did this IRB come back to you with any questions about the protocols, any questions about—

Mr. KUTZ. Their initial focus was on the consent form, and they wanted us to, if you will, dumb it down so 5th grade level of reading could be done, so they were very focused on the consent form, which is part of their—not a lot of substance on the actual medical or the issues of the hospitals, who were these surgeons, who is this person actually putting the item into the woman's pelvic region after open surgery, no questions at all of substance like that.

Mr. WALDEN. My time has expired.

Mr. STUPAK. Thank you, Mr. Walden. Ms. DeGette for questions, please.

Ms. DEGETTE. Thank you, Mr. Chairman. Mr. Dueber, how long has Coast been in business?

Mr. DUEBER. Since 2002.

Ms. DEGETTE. Since 2002. And since that time, you have reviewed 352 protocols, correct?

Mr. DUEBER. No. I don't know exactly how many we have reviewed.

Ms. DEGETTE. OK. Have you declined any of the protocols that you have reviewed?

Mr. DUEBER. My understanding is yes, but I don't know how many.

Ms. DEGETTE. OK. Mr. Chairman, I would ask unanimous consent that Mr. Dueber supplement his response to tell this committee how many protocols that they have reviewed and how many they have approved and how many they have rejected.

Mr. STUPAK. Without objection.

Ms. DEGETTE. Thank you. Now with this particular protocol you took this on 5 months ago, correct?

Mr. DUEBER. Correct.

Ms. DEGETTE. And you approved the protocol for testing on humans within 48 hours, didn't you?

Mr. DUEBER. On this particular study, I am not sure what the turnaround time was.

Ms. DEGETTE. Well, your company advertises a 48-hour turnaround on most cases, correct?

Mr. DUEBER. What that refers to, ma'am, is that—

Ms. DEGETTE. Yes or no.

Mr. DUEBER. I can't answer yes or no because I need to explain it.

Ms. DEGETTE. All right. Go ahead.

Mr. DUEBER. The turnaround time refers to the amount of time it takes for the Coast administrative staff, which is separate from the board, to review the documents presented by the protocol sponsor and—

Ms. DEGETTE. OK, I got you. So it is the administrative turnaround. How long and on average per protocol does it take you to approve this protocol for human testing?

Mr. DUEBER. I am not sure because the board—every member of the board has to review thoroughly the protocol.

Ms. DEGETTE. So can you give me—how long did it take on this case? Did it take 48 hours to approve it for human testing on this case?

Mr. DUEBER. Well, it probably took longer than that because—

Ms. DEGETTE. Well, how much longer?

Mr. DUEBER [continuing]. There were two board—

Ms. DEGETTE. Three days, 4 days, 5 days?

Mr. DUEBER. Well, there was a week between the preliminary approval and the final approval.

Ms. DEGETTE. A week. OK. Now, excuse me, sir, we can swear in your lawyer if he would like to testify, but I would like you to answer. Now so it took a week to approve this protocol. At the time that the protocol was approved for human testing, the report that was prepared by this very fine doctor that you talked about, did he prepare that report at that time that the protocol was approved?

Mr. DUEBER. Are you referring to the minutes of the board?

Ms. DEGETTE. I am referring to the Kupeck Group LLC report that you provided to this committee late last night.

Mr. DUEBER. You are asking how long did it take him to do this?

Ms. DEGETTE. No. I am saying did he prepare this at the time, 5 months ago, when it was approved?

Mr. DUEBER. No.

Ms. DEGETTE. No. Was there a written report by him approved that went through all the scientific basis 5 months ago?

Mr. DUEBER. No.

Ms. DEGETTE. Was there anything in writing analyzing the scientific evidence and the risk and benefits?

Mr. DUEBER. There was extensive discussion at the board meeting itself between—

Ms. DEGETTE. Was there any written report prepared at that time?

Mr. DUEBER. There were minutes prepared for that.

Ms. DEGETTE. Does this committee have copies of those minutes?

Mr. DUEBER. Yes.

Ms. DEGETTE. OK. I would ask our committee staff if I could get a copy of those minutes, please. Now this report, when was this prepared, the report that you keep referring to as to the scientific efficacy of the protocol, prepared?

Mr. DUEBER. Yesterday.

Ms. DEGETTE. And why was it prepared yesterday?

Mr. DUEBER. Because we contacted—

Ms. DEGETTE. Because you were coming in to testify today, right?

Mr. DUEBER. We contacted this individual and asked if he would review this because we were—

Ms. DEGETTE. Because you were coming in to testify today, right?

Mr. DUEBER. Well, we were convinced because Dr. Dodd was convinced that this substance was safe. He made that determination. The board agreed. We have five doctors, high quality doctors, on our board, and they agreed it was safe.

Ms. DEGETTE. OK.

Mr. DUEBER. We just wanted before we came here to find out if that was—

Ms. DEGETTE. To find out, in fact, if it was safe?

Mr. DUEBER [continuing]. In fact the case.

Ms. DEGETTE. We could have been doing human testing for 5 months without that report.

Mr. DUEBER. But, ma'am, no one in—we have never at Coast ever had a fraudulent study submitted to us. There is no economic reason for anybody to do such a thing.

Ms. DEGETTE. OK. I am sorry. First of all, let me stop you and say I now have the minutes in front of me, and the whole discussion is about a paragraph long. But as the chairman is saying, the paragraph never talks about what is in that 95 percent of the substance, so how would they possibly know if this would be safe?

Mr. DUEBER. It is based on propylene glycol which is proven to be safe.

Ms. DEGETTE. But that is 2.5 percent.

Mr. DUEBER. Propylene—

Ms. DEGETTE. What is in the rest?

Mr. DUEBER. The board reviewed that and felt that it was safe and there was—

Ms. DEGETTE. OK. I am going to—

Mr. DUEBER. —a 510(k) device upon which they were basing, you know, the fact that that existed and therefore it should be safe. And, of course, we didn't check the 510(k) device to see if it was real, but we never had reason to do that, ma'am.

Ms. DEGETTE. Let me just stop you. Now Ms. Christensen-Green and I are sitting here looking at this going we sure don't want this in our abdomens, and I think all the other women sitting here today are thinking that. That is the thing about IRBs. We think that when we approve—when we ask IRBs to review a protocol, we are doing it so that they can review the safety of the entire protocol. And we have had situations like this where—we had one situation where an IRB approved a protocol where they performed one type of plastic surgery on one-half of someone's face and another type on another half, and that person was grossly disfigured. What would have happened if this actually would have gone into human testing, and they would have put something poisonous as the other 97.5 percent into women's abdomens?

Mr. DUEBER. I can't speculate on what would have happened.

Ms. DEGETTE. I can't either. Dr. Menikoff, would you agree that is a problem?

Dr. MENIKOFF. Congresswoman, this study is outside OHRP's jurisdiction. It was not federally funded.

Ms. DEGETTE. Well, I understand that, but if there was a study that put 97.5 percent of a substance as part of a human trial into someone's abdomen, that would seem to be a problem?

Dr. MENIKOFF. Again, this is not under our jurisdiction. I think FDA is in a better position to comment on the facts. We saw no protocol.

Ms. DEGETTE. So you don't—OK. Dr. Less, what is your—

Ms. LESS. We have not seen the protocol or device description either. We would need to know what is in the product before we could comment.

Ms. DEGETTE. Right, but you certainly wouldn't think that—you certainly wouldn't approve some kind of a drug that put a whole bunch of fluid like this where it wasn't specified what it was as part of a surgical operation?

Ms. LESS. We would need to know what is in the product, how it is being used, a full device description.

Ms. DEGETTE. I just have—

Mr. STUPAK. No, no, we got to move on. We have both former chairs who would like to ask questions. Mr. Barton for questions, please.

Mr. BARTON. Thank you. You talk about a target rich environment for questions. My first question is to our representative from the GAO. The protocol and the device that you all chose, you, not you personally, but your organization consciously picked one that the FDA had already rejected and then changed it to make it even worse, isn't that correct?

Mr. KUTZ. We picked something that was available on the Internet and altered it significantly. The 3 components of the actual gel, we made up from stuff on the Internet so we had never mixed it together. I can't—we don't know if it works or doesn't work. We just put it together on paper.

Mr. BARTON. But you tried to make it very easy for anybody that was really trying to review the protocol to figure out that it was terrible and reject it, which 2 of the IRBs did.

Mr. KUTZ. Yes. We didn't know what we were doing.

Mr. BARTON. And then this one rubberstamped it almost before they got it, is that a fair statement?

Mr. KUTZ. Well, they actually—I mentioned a coupon in the opening statement. They gave us a pre-review with the coupon and then the final review was where they authorized the informed consent and than the actual protocols.

Mr. BARTON. How did you pay for their review?

Mr. KUTZ. Well, we gave them our credit card number. As it turns out, they never actually charged us.

Mr. BARTON. Really? I would have thought they would have cashed the check almost as quickly as they certified approval.

Mr. KUTZ. We were surprised they didn't. Everybody else did.

Mr. BARTON. Dr. Less and Dr. Menikoff, what can be done to decertify this company right now? Why are they still in business?

Ms. LESS. Again, we don't have the—we have not seen the GAO's report to be able to comment on what actually transpired.

Mr. BARTON. I am not asking you about that. I mean I am so mad at the company, I can hardly be civil, but I am almost as upset with our government folks who are supposed to oversee these IRBs, and this company has gotten 4 or 5 notice letters in the last 2 to 3 years, and yet they are still in business, and they have the gall to come here and threaten to sue the government. They ought to have their butt being kicked out the door within the week.

Ms. LESS. I could provide some background to you on how the process would generally work for a product such as this. This would be considered a significant risk product subject to FDA's jurisdiction that would require an investigational device exemption in order for the study to proceed.

Mr. BARTON. So basically as the representative of the FDA you just say business as usual.

Ms. LESS. No.

Mr. BARTON. These folks are going to stay in business for another 4 or 5 years, maybe approve a product that kills some innocent person, and then we will have another oversight hearing 3 or 4 years down the road. What steps are being taken right now to decertify these charlatans that raised \$4 million in revenue last year scamming the public?

Ms. LESS. Congressman, what I wanted to explain to the committee is that for significant risk products such as this there should have been FDA oversight as well as IRB oversight.

Mr. BARTON. There wasn't.

Ms. LESS. No. This product should have been submitted to the FDA so we could have reviewed the product, looked at what it was made of by compatibility testing, sterility testing, all of that. That piece of this picture was not part of the operation, so that piece of the human subject protection was not invoked.

Mr. BARTON. As the FDA representative, what are you going to do to use whatever enforcement mechanisms the FDA has to hold this particular IRB company accountable?

Ms. LESS. We would have to go and look at—

Mr. BARTON. What are you going to do?

Ms. LESS. We need—

Mr. BARTON. Are you going to do anything at all? Are you going to make a report? Are you going to make a recommendation?

Ms. LESS. We will take the information from the GAO, fully evaluate it, do our own investigation and see what needs to happen.

Mr. BARTON. You will do that?

Ms. LESS. We need to see the GAO's findings and see exactly what happened and evaluate it and see what we need to do.

Mr. BARTON. Do you have any sense of outrage about this?

Ms. LESS. Without knowing exactly what went on—

Mr. BARTON. So the answer to that is, no, you don't?

Ms. LESS. We do. We are very concerned with human subject protection.

Mr. BARTON. Dr. Menikoff, you represent HHS. Do you have any sense of outrage about this? Are we the only people—the people that are elected, are we the only ones that seem to be—

Dr. MENIKOFF. First of all, I would certainly welcome on OHRP's behalf obtaining information about what happened. We have yet to see any actual information or documentation of what happened. We would welcome obtaining that and reviewing it and taking appropriate action.

Mr. BARTON. So you are in a passive mode also? If we bring a dump truck load of documents, you will review them? Are you going to be an advocate for investigation, use the authority of the Health and Human Services?

Dr. MENIKOFF. OHRP is an advocate for improving the protection of research subjects. Again, nobody has provided us yet any document that information about what happened. We welcome that. We are eager to get it even before this hearing, and we would welcome receiving it, and we have appropriate procedures to protect sub-

jects, and we would implement those procedures and determine appropriate action.

Mr. BARTON. Well, my time has expired, Mr. Chairman, but I am outraged, and I am going to encourage you and Mr. Waxman and Mr. Walden to use every authority of the United States Congress and the Energy and Commerce Oversight and Investigations Subcommittee to eliminate these bad actors. I have a sister-in-law who is undergoing cancer therapy treatment. She is Stage IV right now. And she is looking at submitting to some protocols for some experimental drugs that would be subject to an IRB approval, and it appalls me, it appalls me, that, you know, it is apparently with the exception of GAO who seems to be pretty intense about this, FDA and HHS appear to be almost indifferent, and of course the IRB president is incense that we are even asking questions. I mean that is just outrageous. So I will work with you, Mr. Chairman, and we will—

Mr. STUPAK. Mr. Kutz, if you want to respond to Mr. Barton.

Mr. KUTZ. Yes. We have actually sent a letter to FDA as of yesterday requesting them to do an investigation. The interesting point is when the letter was sent by the committee and Coast made the allegations against us, FDA had an investigator with the U.S. Attorney to go after charges after our fake company, so they were very aggressive at that point in time—

Mr. BARTON. Bless their little hearts.

Mr. KUTZ [continuing]. About going after—without any evidence except a letter from Coast they were ready to go to the U.S. Attorney to go after us, so I just wanted to make sure you understood that, Mr. Barton.

Mr. BARTON. We have a company here that has received three or four notice letters in the last several years. I mean it is just ridiculous. I yield back.

Mr. STUPAK. We thank the gentleman. Our hearing is going to continue. As the former chairman noted earlier, this is our second hearing on IRBs and something we have an interest in. There will be legislation. I know Ms. DeGette has legislation. There will be other legislative proposals after this hearing, I am sure. We have seven votes on the floor. I am going to ask members' patience and ask them to come back in approximately 1 hour. We will be in recess for 1 hour, and then we will come back and continue this hearing. Thank you.

[Recess.]

Mr. STUPAK. This meeting will come back to order. Witnesses are reminded they are under oath. And, Mr. Dueber, Ms. DeGette, hopefully she is going to come back, but she had asked you if it was your policy to prove the protocol to board members within 24 or 48 hours. You said, no, it was longer. She asked specifically about this one but under testimony before the committee the record should reflect on page 27 the question was you tried to do this once if a protocol goes to the board or board members turn around and make a decision within 24 to 48 hours, is that correct? Your answer was right, right, yes.

Mr. DUEBER. Yes. I checked into that. Again, I am new to the company. I have been there 5 months.

Mr. STUPAK. Well, you shouldn't be new to the truth. Either it is yes or not. I mean you have your testimony. Your attorney has it. Just a caution, that is all.

Mr. DUEBER. I was not intentionally telling—

Mr. STUPAK. I didn't think so. OK. Ms. Christensen for questions, please.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman. This is one of my first hearings on the Institutional Review Boards, and I am really shocked at some of what I am reading and hearing. And I am concerned that the IRB can be listed and then utilized by researchers without the Department of Health and Human Services even having to do a cursory check and that if federal funds are not involved or an FDA-regulated product is not involved there doesn't have to be any federal oversight or research if I am understanding correctly. And I also wonder listening and reading if there should even be private for-profit IRBs. Maybe they ought to be university-based or somehow more directly under the purview of the department.

My first question, I will begin with you, Mr. Dueber. When the committee staff interviewed you last week, you acknowledged that your company did not verify the physicians leading these experimental studies or that their credentials were accurate. In fact, when the GAO submitted its fake protocol to your company you didn't verify that Jonathan Kruger, the person listed as the primary clinical investigator, in fact, had a legitimate medical license, is that correct?

Mr. DUEBER. Yes. What we did was we have never had the experience of having a fraudulent group of people lying to us about their existence and about their licenses. They did submit a license copy but it turned out to be fraudulent too. So what we have learned from this is we need to start checking that. We have changed our SOPs accordingly, but we did in our review what was required by regulations, and regulations do not require that that be done but regardless of whether it is required or not, we are doing that now.

Mrs. CHRISTENSEN. But you did eventually once you were asked to testify checked on the doctor. How long did it take for you to make that determination?

Mr. DUEBER. Well, this whole thing didn't come up until I got the letter from the subcommittee on the 23rd of February so some time after that, a day or two after that, we started checking into—

Mrs. CHRISTENSEN. Was it a long process to check to determine whether he was—

Mr. DUEBER. Well, the date that sticks in my mind where most of the work was done was March 5, and it took a team of us about maybe 3 to 4 hours to check all these things out, the existence of the company which didn't exist, the phone numbers, the licenses, and all that. It took quite a bit of time to just go—

Mrs. CHRISTENSEN. For all of it, but probably checking to see whether the doctor was a duly licensed physician—

Mr. DUEBER. That doesn't take long. That is why—you know, that is prime example of why we are going to start changing that and start doing it.

Mrs. CHRISTENSEN. Mr. Kutz, let me turn to you. You submitted a fake medical license to Coast IRB on behalf of Dr. Kruger. I think

it is in the binder that you might have there. It is tab 2. It is the State of Virginia. The date on the license is 1990.

Mr. KUTZ. That is correct. I don't have the binder but that is correct.

Mrs. CHRISTENSEN. But Virginia requires medical doctors to obtain a new license every 2 years like most places do so this 19-year old license would have expired back in 1992. Isn't that something that the IRB should have caught?

Mr. KUTZ. Since they weren't looking at that, I guess they wouldn't have caught it, but certainly if they understood that they had to be done every 2 years that would be something that they could put in their protocols.

Mrs. CHRISTENSEN. Well, Mr. Dueber, how come the company did not catch the fact that this was an expired license? I am a physician, so I am very sensitive to issues relating to physicians.

Mr. DUEBER. I don't know. I wasn't there. I don't know why it wasn't caught.

Mrs. CHRISTENSEN. But you would agree that if a doctor had engaged in malpractice or had lost their license that it would be the job of the IRB or Coast in particular to check that?

Mr. DUEBER. After this experience, I would agree, yes.

Mrs. CHRISTENSEN. And you would agree that if you realize that that license had expired 19 years before that you would—would you have approved that study if you had picked up that the license had expired or that the person—well, that the license had expired, just simply that?

Mr. DUEBER. Well, that is speculating but if someone submitted something like that and then it had expired we would do a lot of other things then to check into the validity of other things sent to us, which could end up resulting in us not taking on the study or not approving it.

Mrs. CHRISTENSEN. But the principal investigator not having a valid license would be a reason to not approve, wouldn't it?

Mr. DUEBER. Yes.

Mr. STUPAK. Gentlewoman, would you yield on that point? This license was invalid on its face, was it not? You didn't have to check. It was invalid, 17 years old, 10 years old, so it was invalid. There was no checking to be done.

Mr. DUEBER. Yes, that is correct.

Mrs. CHRISTENSEN. My time has expired, Mr. Chair. Thank you.

Mr. STUPAK. Any other questions?

Mrs. CHRISTENSEN. I did have another one.

Mr. STUPAK. Go ahead.

Mrs. CHRISTENSEN. OK. To Dr. Less. In April of 2007, well before our investigation of Coast began, HHS received a letter containing allegations about Coast. They turned the letter over to FDA because the accusations related to FDA-related research. FDA initiated an inspection of Coast in July, 2007. In March, 2008, FDA issued a warning letter to Coast finding that Darren McDaniel, who was the CEO at the time, improperly assigned someone with only a high school education to conduct an expedited review of a human testing protocol.

Dr. Less, I think it is commendable that the FDA took action to investigate and address this allegation, but as the GAO investiga-

tion has shown, Coast had numerous other problems including a review process that approve protocols based on a 19-year old medical license, board members don't read protocols, and these coupons that explicitly encourage IRB shopping. Why didn't FDA identify some of these other clear deficiencies at Coast?

Ms. LESS. Congresswoman, FDA, when they go out and do an inspection they generally spend a few days inside and they pull two or three studies, follow those studies from approval through continued review, look for adverse events, see whether or not the IRB had appropriately addressed those adverse events or changes to the protocol. When we went out on this, it was a for complaint—a for-cause inspection. We had been out there several times before, had not identified problems. So for this case we went out specifically to look into the allegations that expedited review had not been used properly, so we were investigating that. And we did issue a warning letter and we imposed sanctions because we had been out there before and had found some minor violations so we imposed sanctions that they not use expedited review anymore.

And generally what we will do when we do issue a warning letter is follow up. We make sure that the IRB institutes a corrective action plan within 15 days. We review that, look to see if it has adequately addressed everything that we were concerned about, and then we put them on our list for follow-up inspection.

Mrs. CHRISTENSEN. So you don't do a comprehensive review generally when you visit an IRB, you just review the specific complaints?

Ms. LESS. It depends on why we are out there because we had been there several times before and had done a more comprehensive review and pulled a number of studies and looked at those other studies. But in this particular case we just focused on the complaint.

Mrs. CHRISTENSEN. But the original letter also identified other concerns including back dating, changing board meeting minutes and not following through with board requests that the FDA inspection investigate those issues while you were there?

Ms. LESS. We did look into all of those. The ones that we identified in our warning letter, I believe, were all related to the abuse of expedited review and potential conflict of interest that the CEO had inserted himself into the process and had inappropriately used expedited review, and so we focused on those issues.

Mrs. CHRISTENSEN. Including the back dating and changing of the board—you did. And, Dr. Menikoff, did the allegations result in an evaluation of Coast's internal practices and procedures?

Dr. MENIKOFF. Are you talking about the current allegations?

Mrs. CHRISTENSEN. No, the ones that I just referred to, the 19 year old doing the expedited review and the backdating, changing board meeting minutes, not following board requests.

Dr. MENIKOFF. Well, Congresswoman, as noted earlier, OHRP and FDA have separate jurisdiction. They began this investigation on a study which was under FDA jurisdiction and was not under OHRP jurisdiction. FDA and OHRP regularly communicate, and we discuss issues relating to actions that one agency or the other takes, and we will deal appropriately and generally do deal appropriately in terms of this.

Mrs. CHRISTENSEN. Well, I am going to stop here but my question really was did you do an allegation as a result of those set of allegations? Did you do an evaluation related to this?

Dr. MENIKOFF. The evaluation was under FDA's jurisdiction at the time, and we would normally at that point—it is the same set of regulations. We would normally allow FDA to conduct an appropriate investigation.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman. I appreciate the additional time. Thank you.

Mr. STUPAK. Thank you. Mr. Dueber, if we go back to that license, that license that was 19 years old, if you could put that back up on the board, could also indicate that maybe the doctor had been malpractice, no longer licensed to practice medicine, could it not, if the license was 19 years old?

Mr. DUEBER. It could have been anything. The fact that we didn't catch that it had expired was something we should have caught.

Mr. STUPAK. Right. Right. And the reason why we are doing these hearings, and I have been on this committee now for 15 years, and Mr. Walden for quite a while too, back in 2002 we had a veteran die during experimental drug testing conducted by someone who was not credentialed to practice medicine in the United States like this Jonathan Kruger technically is not because his proof of license is 19 years old. So your responsibility as an Institutional Review Board is to do due diligence to protect the health and safety of the patient. You are the gatekeeper between medicine and the patient. And you testified earlier you had four—I think you had five, you have four doctors and one registered nurse and two other people in reviewing this. I am baffled as to why there is no due diligence and why things like this are not caught.

If I had four doctors looking at a license, I think someone would have caught it. You might talk about 2½ percent of Adhesiabloc but 97.5 percent of it, we don't know what it is, and then you are going to put this in a lady's abdominal cavity but not by the doctor who performed the surgery but by an assistant according to the protocol, and the doctor wouldn't even know. And if I was a patient and I became sick after you dumped this liter bottle in me, I would go to the doctor, and the doctor who performed the surgery wouldn't know anything about it because the protocol was real specific that the doctor had to be out of the room when they applied the Adhesiabloc gel to the patients. I would have thought someone—I am not a doctor, but I thought that is pretty strange, isn't it, because when I get sick, where am I going to go? I am not going to go to the assistant who put the gel in me because I don't know who it is because I am under anesthesia and I am out. I am going to go back to my doctor. My doctor isn't going to know anything about it according to this protocol. That is crazy, isn't it?

Mr. DUEBER. I spoke further with Dr. Dodd, and he told me that he was familiar with a product called Hisken. He said it is a similar product used in surgeries, and is added to the abdominal cavity in the same relative volumes as the protocol here. Dr. Dodd said he is very familiar with Hisken and was comfortable with that volume so—

Mr. STUPAK. But you never verified the 510(k) process to see what this junk is I am dumping in the woman's body. You never

looked. Now there might be something out there that maybe in the surgical field someone may use but remember you are the gatekeeper. You are the person who is protecting the patient from some doctor whose license is 19 years old and you are the gatekeeper, so just because there might be something out there but since you don't know what 97.5 of this stuff is, you really can't say it is safe.

Mr. DUEBER. Well, that is precisely why after having experienced this whole episode that we have gone through, we have changed our SOPs to check the 510(k), to check on the predicate device it is based on, to check the doctor's credentials, to check the existence of the company.

Mr. STUPAK. So what about the—you said you have done thousands of these trials. Currently you are in 70 clinical trials. Did you do those in those others? Did you check the doctor's credentials? Did you check to see what the licensing regulations are, the 510(k), whatever you call it?

Mr. DUEBER. We did not, and, you know, we have never had a fraud like this perpetrated on us. We have had—

Mr. STUPAK. It is not a fraud on you. You didn't do your work. We caught you. That is all. It is not a fraud. Where is the fraud?

Mr. DUEBER. No, that is incorrect, sir. We did our job. We did what FDA regulations require.

Mr. STUPAK. Really? I thought you said your job was to do due diligence and protect the patient. How did you protect the patient in Coast's IRB with this protocol?

Mr. DUEBER. We were following the regulations that were outlined in the FDA's regulatory—

Mr. STUPAK. Does the FDA license say—regulations say you have to check the credentials of the doctor?

Mr. DUEBER. No.

Mr. STUPAK. Does it say you have to check the substance?

Mr. DUEBER. We never had to, sir, because we have never had anyone try to—

Mr. STUPAK. What expertise do you have, if you say now when you are caught, well, the FDA didn't tell me to do this, but the FDA doesn't tell you the basic stuff, so what is the expertise of your Coast IRB to even run to review protocols? If you can't catch simple things like this and if the FDA doesn't tell you and you can't think of it, what qualifications then do you have to be an IRB?

Mr. DUEBER. We have a great deal of qualifications. We have got some outstanding very educated, very experienced doctors and nurses and laypeople on our board.

Mr. STUPAK. Then why didn't they catch it? You had more medical people, and I have looked at a lot of IRBs, of the seven people, five of the seven have medical backgrounds and they never catch any of this stuff. That is amazing, especially since our protocol, as testimony was earlier, Mr. Kutz had indicated, is truly based on a real study of a product that killed people.

Mr. DUEBER. Our review—well, this product wouldn't kill people, and we know that. Our procedures are—

Mr. STUPAK. Tell me what is in this bottle. How do you know this won't kill anybody?

Mr. DUEBER. I am not a scientist. I can't answer that.

Mr. STUPAK. Well, you keep saying this product wouldn't kill anybody, Adhesiabloc wouldn't kill anybody. You don't even know what is in it. See, that is the part that baffles us up here. You act like you did nothing wrong, it would not harm anybody, but you don't know what is in here. Isn't that your responsibility again to protect the patient? Isn't that your responsibility? How can you protect the patient if you don't know what is in it? I mean the other two IRBs that we have spoke of and Mr. Kutz has talked about, man, that just said this is crazy. You shouldn't do this. There is no patient safety. We don't know what the substance is. No one should do this. And then when they finally realize someone approved it, they said, oh, boy. That was your famous quote, I think, there, Mr. Kutz.

Mr. DUEBER. We have had—you know, Dr. Dodd was the original expert that reviewed this, and now we have this other outside party that reviewed it who is an expert and—

Mr. STUPAK. This outside party, did he review—he reviewed Adhesiabloc, he reviewed this, your expert there you mentioned?

Mr. DUEBER. The expert reviewed that, yes.

Mr. STUPAK. Oh, yes? What is in here? What does your expert say is in here?

Mr. DUEBER. I don't have his report in front of me.

Mr. STUPAK. You just paid for another bad report because no expert has ever reviewed this. You know why? Because we made it up last night. There is 2.5 percent, the stuff on the top, we made this up. So if your expert—if you paid someone money to review this they never contacted us to get what the contents we are talking about. How can you review something if you don't even know the chemical formula of the stuff you are supposed to be reviewing? Let me ask you this. Let me ask you something you should know something about. This is your coupon that Mr. Kutz testified to that was delivered to him after you had your first contact with him where Coast, here is your coupon, good for one time research protocol review worth \$1,300. Take a free test drive on us. And here is the back of your coupon.

So let me ask you, take a free test drive. There is a picture of a car and all that here, and there is a smiley face looking—here is the car. Here is the smiley face looking at me in the rear view mirror in my car, and it says coupon good for one time research protocol review worth \$1,300. And then it says coast through your next study. So it sounds like to me that your study is more likely to be approved if you go with Coast. Am I reading that wrong?

Mr. DUEBER. No—yes, you are reading it wrong because what that is is a marketing piece. It is just trying to get different companies, new companies, to try out Coast and try out Coast's customer service. You know, there is nothing wrong with using some kind of a promotion to gain new business. It doesn't have anything to do—this is the business side of the business. This has nothing to do with the review board and the decisions they make. Those are 2 separate businesses.

Mr. STUPAK. Coast through your next study. We coasted through in 48 hours and there are all kinds of problems with our study, right?

Mr. DUEBER. We are not using that marketing piece anymore but, you know, that is just a piece that was used to try to generate some new business. It has nothing to do with the actual review of the studies. That is done by a separate review board that are independent contractors, and they have nothing to do with the business side. They don't know anything about money that we make or money that we don't make. They are not—

Mr. STUPAK. Well, speaking of the money you make, you made what, grossed \$9.3 million last year. At \$1,300 a pop, that is a heck of a lot of reviews.

Mr. DUEBER. Most of them are a lot more than that because that is a single study rate. You know, there are protocols that have hundreds of sites, generate a lot more revenue because there is a lot more work involved to review it.

Mr. STUPAK. Sure. Let me ask FDA or HHS, how many Institutional Review Boards come on line every month?

Dr. MENIKOFF. Each month we process about 300 applications. Some of those are amendments or renewals.

Mr. STUPAK. So basically how many are new ones a month?

Dr. MENIKOFF. I don't have an exact number on that.

Mr. STUPAK. Are you concerned that people are seeing this as sort of a quick way to get rich? Do you need 300 a month? That is 3,600 a year.

Dr. MENIKOFF. Again, Mr. Chairman, many of those are likely to be amendments or renewals of an existing IRB.

Mr. STUPAK. But don't you think we should have some kind of limitations on IRBs? Shouldn't they have some qualifications before you become an IRB?

Dr. MENIKOFF. If you would like me to address the registration system, the registration system that OHRP runs was put into place as a result of the OIG 1998 report. The goals of the registration system were modest to have a list of the number of IRBs out there and to have some contact information.

Mr. STUPAK. This is your registration system. This is Trooper dog, remember, at Maryland House?

Dr. MENIKOFF. Mr. Chairman, the system is such that we verify that people put in the information for requested piece of information.

Mr. STUPAK. Really? How do you verify it with Trooper dog here?

Dr. MENIKOFF. By registering an IRB the government, federal government, is in no way endorsing that IRB or in any way saying that IRB—

Mr. STUPAK. Don't you think when an IRB is registered with the HHS there is sort of like a seal of approval authentic because I have this approval, like fake medical devices sent up by Mr. April Fuhl.

Dr. MENIKOFF. OK. Mr. Chairman, again, we in no way—the system is not designed to be any endorsement of an IRB, nor do we intend it to be, and to the extent any of the evidence you revealed during this hearing or the GAO has revealed—

Mr. STUPAK. Yes, but my question was doesn't it give people an aura of authenticity because you—

Dr. MENIKOFF. I understand that. We were not aware that this was a problem that people out there were thinking—

Mr. STUPAK. Really?

Dr. MENIKOFF [continuing]. Because an IRB was registered that the federal government was endorsing it. The federal government has many systems by which it has lists of—again, this is sort of like a contact phone book.

Mr. STUPAK. This is an IRB that is supposed to be set up to protect patient safety. This isn't a phone book.

Dr. MENIKOFF. I understand that, and there are many parts of the system that actually help ensure that IRBs are operating appropriately. The registration system—

Mr. STUPAK. Tell me one thing you do after you register an IRB, what do you do to make sure they are valid IRBs or doing it properly?

Dr. MENIKOFF. OHRP has several divisions that work at this. We have a compliance division that we accept reports of non-compliance from anybody who wants to report.

Mr. STUPAK. So nothing until somebody complains like if someone dies?

Dr. MENIKOFF. If you are asking whether the current system basically puts a stamp of approval on an IRB at the moment it is created, it was not designed to do that.

Mr. STUPAK. Mr. Kutz, what did your investigation find when people would register? Was that a seal of authenticity, approval or something? Why did you undertake that part of registering fake IRBs with HHS?

Mr. KUTZ. Obviously, he is saying it is not intended to, but one of the IRBs, for example, that we submitted our protocols to, said that it gave us an aura of legitimacy. And so, yes, I believe people out there would—and plus it is called assurance, but it is really self-assurance, and so it doesn't really provide anything except registration, as he said, of what is in the system. So maybe we shouldn't be calling it assurance either. It depends on how you perceive that. I could perceive assurance to mean someone has actually reviewed and approved an application.

Mr. WALDEN. Mr. Chairman, will you yield on this point because I thought the CFRs, the regulations of the federal government in 45 CFR part 46.101(d) state that as part of evaluating assurances the department "will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research." Is that not part of your rules?

Dr. MENIKOFF. Yes. Now that rule dates back to 1974. It was implemented at a time when this whole system was first being created and people didn't understand the complexity of how the system works, how you best protect research subjects, and how an IRB should function. Over the decades as the system was implemented, people discovered basically that the efforts being spent in implementing that provision essentially amounted to verifying, for example, that an IRB that reviewed medical type studies had one or two doctors on it, and a lot of effort was being spent at assuring that fact. This was then reviewed by the OIG in the 1998 report I described, and it actually concluded that the way that provision was being implemented was not actually advancing human protections, that a better way to do this was to create a more streamlined system that basically what you needed was—

Mr. WALDEN. And we are 10 years later, and that system is due to come on line this summer?

Dr. MENIKOFF. No. Part of that system have already been implemented.

Mr. WALDEN. And so if you had had to follow this regulation that is still on the books, correct?

Dr. MENIKOFF. Yes.

Mr. WALDEN. Would not that check of assurance to make sure that the fake IRB created by GAO was legitimate, wouldn't that regulation have caught that? These folks listed themselves as from a city in Arizona named Chetesville. I mean come on. Do we have nothing in place that would have caught a fake IRB?

Dr. MENIKOFF. Congressman, the system is currently designed in a way that you gave a registration with some cute names that again had spelling errors and other things that unless somebody sat there and tried to pronounce the names and the addresses, they would not pick up the things that seem incredibly obvious right now, and the system wasn't designed to do that. We do not have our staff going through the names to see whether people have put funny names on the list, nor indeed would we know what—

Mr. WALDEN. So what good is it to register with your agency when you put a stamp of approval on an IRB that then is system wide usable for others to go through to certify human tests? Is it a pointless purpose?

Dr. MENIKOFF. Congressman, we are not putting a stamp of approval on the IRB. If the federal government—

Mr. WALDEN. But people market it that way. We have examples of advertisement where they say, this one, I won't read you the name, you can count on IRB standard for high quality review and documentation, full AAHRPP accreditation, good standing with FDA, registered with OHRP.

Dr. MENIKOFF. OK. And, again, it is mentioning several other entities. One of those is AAHRPP which is an accreditation entity that is in the business of accrediting IRBs. But in terms of the federal government aspects of this, we are not in the business currently—that would be a different system, and we welcome your input in terms of whether or not you think that would be a good thing to do. That would be a dramatic change from the system. The system is never designed to basically have us from the outset endorsing and putting some sort of stamp of approval—

Mr. WALDEN. So you think the system works well today?

Dr. MENIKOFF. Right now we think we have a well-functioning system. There is certainly room for improvement but in terms of the part of the system that OHRP deals with, it is interesting that GAO, for example, we deal with the funded studies. GAO was not able to create a fake study that went through and got federal funding.

Mr. WALDEN. No, but GAO could have created a privately—a study through private funding that would have your HHS stamp of approval on an IRB, right?

Dr. MENIKOFF. Again, it is not a stamp of approval. It is a registration.

Mr. WALDEN. Well, you don't call it that but you could say I am registered with HHS.

Dr. MENIKOFF. You are a problem. We welcome the information and we will look into this in terms of making sure that people out there know that the government currently is not putting a stamp of approval. It is a registration list. Anybody could sign up on the list. That is exactly what—

Mr. WALDEN. Clearly.

Dr. MENIKOFF [continuing]. OIG intended when it asked for this list to be created. They wanted a quick and dirty way to put people on our list so we would know vaguely how many IRBs are out there and contact information.

Mr. WALDEN. Mr. Kutz.

Mr. KUTZ. Well, I think the Federalwide Assurance which includes the IRB and the medical device company, this is necessary for federally funded research so it is, I assume, meaningful for federal people applying for federal grants with, I believe, 19 agencies, so I would believe those agencies potentially put some credibility behind people that have Federalwide Assurance.

Mr. WALDEN. Because what you are getting when you register with Mr. Menikoff's office is Federalwide Assurance.

Mr. KUTZ. Correct, for federal funded projects.

Mr. WALDEN. That is the gate. You got to get through that gate in order to even go to the next step, right?

Mr. KUTZ. Correct.

Mr. WALDEN. And then there may be a check or balance that catches you there?

Mr. KUTZ. There could be beyond that, yes, but just to get that—you have to get that to even apply is my understanding.

Mr. WALDEN. So it does serve more than just a place to register to get mail for future conferences or other updates. It is actually something that is required elsewhere in the government?

Mr. KUTZ. For federally-funded projects, not for privately funded. That is my understanding.

Mr. WALDEN. Do you disagree with that?

Dr. MENIKOFF. OK. If I could clarify, we are talking about two things here. There is a registration system which is a registry, a list of some information about each IRB. There is an assurance process, the Federalwide Assurance. They are different things. The registration list, yes, an IRB to be used by an entity that wants to get federal funding or HHS funding has to be listed on the registration list. If I could describe the Federalwide Assurance, that is essentially an agreement by which before you take federal funding, you have to agree, you have to sign on the dotted line that your entity agrees to abide by the federal regulations. So essentially by getting Federalwide Assurance an entity is actually committing itself and putting itself under a legal burden that it will abide by the regulations.

The federal government is in no way endorsing the entity, but it is just that a federal funding agency at HHS cannot give funds to them until it has basically sworn and said, yes, we will protect human subjects. We agree that we will have to abide by the federal regulations. That is a good thing, and the intent of the system is to encourage, make sure people could get Federalwide Assurance and could basically be willing to swear that they will indeed abide by the federal regulations.

Mr. WALDEN. I will tell you, I guess when I get back home and try and explain how you register an IRB or whatever you want to call it, and it is up here on the chart, fake medical device, easy reviews. They are clever names, I don't doubt that. And that that gives you then the authorization to oversee the protocols on the human tests and that that seems to be all it takes.

Dr. MENIKOFF. If I could clarify, in terms of the jurisdiction side that OHRP deals with a major part of the picture has been left out, which is that the IRB is not working in a vacuum. As we noted again, GAO was actually not able to get federal funding. An IRB reviewing a study, is it hard to get federal funding.

Mr. WALDEN. But they did get approval on the other side of the coin. They were able to go to an IRB and get approval for human tests.

Dr. MENIKOFF. Yes. And I am just pointing out an IRB that is reviewing a study that is getting federal funding, getting federal funding itself involves a very detailed process of checks and balances—

Mr. WALDEN. I understand that.

Dr. MENIKOFF [continuing]. That again that is a part of the research world that is under OHRP's jurisdiction. Much of the vetting that you are concerned about will actually happen, for example, before NIH gives funds. Barely 20 percent of the studies actually get funded these days. It is very competitive. These things are reviewed by panels of the most eminent—

Mr. WALDEN. So you don't see that there is any real problem with what you have learned from GAO, is that—

Dr. MENIKOFF. Up to now, everything you have indicated GAO has done, I would think would be highly problematic for that to have happened in terms of the studies that get federal funding. Again, we are open to looking at the information on what happens but—

Mr. KUTZ. We didn't apply for federal funding and I am not sure—and I don't think we actually would because we might actually displace a legitimate applicant so that would not be necessarily an appropriate undercover test in this case, but we didn't apply. So I am not sure if we couldn't but we didn't apply, and I assume there are a lot of other controls there that would have had to have been tested, but just for the record we did not try to get federal funding. We just used this to give us an aura of credibility up there amongst the people that were medical device and IRB companies.

Mr. WALDEN. So where in your fake IRB ad, you felt like you got that stamp of approval, and it meant something in the marketplace when you advertised?

Mr. KUTZ. We used it as that, and certainly again as I mentioned at least one of the IRBs that we sent our protocols to said it gave us legitimacy. And I understand what HHS is saying here, but that is the perception out there, so that is an important—whether they like it or not that is what the reality is out there amongst people.

Mr. WALDEN. Thank you, Mr. Chairman.

Mr. STUPAK. Mr. Burgess, questions?

Mr. BURGESS. Thank you. Mr. Dueber, let me just ask you, was this product ever used? Are there any patients who received this product?

Mr. DUEBER. No, not that I know of.

Mr. BURGESS. The board approval came in October, the end of October.

Mr. DUEBER. The first approval did and then November 6 they approved the total project including the ICF form.

Mr. BURGESS. But no patients had been enrolled? Is there any way to know that absolutely for certain?

Mr. DUEBER. No. We have not—we did not receive any SAEs or PD, protocol deviations, or anything of that sort like a sponsor would be required to send us if there was a need to send that to us.

Mr. BURGESS. But say there wasn't any protocol deviation. Say everything went just as smooth as silk. Would you know that a patient had or had not received the 4 250 milliliter vials of stuff?

Mr. DUEBER. Not until we did a continuing review, which the board set for 6 months later, which would be next month, then we would have to go back and have resubmission to us of all the documents. It basically is a full review again of the protocol and the ICFs and what not.

Mr. BURGESS. Well, Mr. Chairman, I am going to ask that that information be made available to us, and I would hope it would be made available to us before a month from now. In light of everything that we have heard today, patient safety should be critical and uppermost in everyone's mind. If we have got people out there who have been treated with a product that wasn't even a product—

Mr. STUPAK. Mr. Kutz could probably answer it.

Mr. BURGESS. That is a real issue.

Mr. KUTZ. But there is no real patients. The whole thing was bogus so there were no people signed up. Now they could have been but they weren't. There were no surgeries performed. Again, everything that we provided was fabricated.

Mr. DUEBER. And on March 6, I might add, we convened the board of our company not knowing that this was still—not knowing what this was, we convened the board and rescinded approval for the study and notified the study sponsor of that, but never could get hold of anyone on the phone or what not. And who we had to send it to was a post office box so it was a phony site to begin with.

Mr. BURGESS. So there was no actual product produced.

Mr. DUEBER. No.

Mr. BURGESS. This looks like a big—

Mr. DUEBER. This was all a big setup.

Mr. KUTZ. We never actually mixed the product together, never, ourselves.

Mr. BURGESS. OK. Now the issue that was of concern to people about the 2.5 percent active ingredient, the propylene glycol, and then I guess 97.5 percent diluent. Do we know, was that just made-up stuff too? There was no actual diluent that was used in those 250 milliliter vials?

Mr. KUTZ. Correct. We didn't say what the other 97.5 percent was. Our protocols were silent on that.

Mr. BURGESS. OK. I will just point out that is unusual to pick a product up off the shelf and not know what the rest of it is because the vehicle is important to—it is important to be aware of

what the vehicle is. Let me just ask you this. If this had gone forward, if this has been a real product or whatever, who would have paid for the surgery? This is a product that could only be placed at the time of an operation, presumably an anesthetic. Day surgery or hospitalization, all of that entails some cost so to get to that point where you can actually administer the product, who was going to pay for the rest of everything else that was happening that day, lab work, hospitalization, day surgery, surgeon's time, anesthesia time?

Mr. DUEBER. I believe the way this was set up was that the patients were people that were going to have surgery anyway, and they would have had to have paid for that surgery through whatever means they had to pay it. They were not receiving—

Mr. BURGESS. OK. Let me just interrupt you on that thought. Would you have actively excluded the patient on the Medicaid system? We made a big deal about no federal funds were used, but would you have excluded a Medicaid patient from this protocol?

Mr. DUEBER. That would have been the sponsor's decision, and we wouldn't have had any involvement in that, so I don't know.

Mr. BURGESS. So there could have been federal funds used in the installation of this product in the peritoneal cavity?

Mr. DUEBER. If it were a real—yes, that could be the case.

Mr. BURGESS. Right. It is hard when you are dealing with a make-up world, and I do understand that and I sympathize with you but we shouldn't be here in the first place, so I am going to press on. The second surgery, the second look operation 20 weeks later, so 6 months later we are going to have another look to see whether or not our product worked, who is going to pay for that surgery?

Mr. DUEBER. I am not sure, sir. I don't know. I don't know.

Mr. KUTZ. I don't believe our protocol said. That was one of the questions we got from one of the other IRBs, who is paying for the surgery, who are the physicians, who are the surgeons, who are the people that are going to actually apply Adhesiabloc to the women's pelvic area. That was all silent in our protocols. Those were serious questions we got from the other IRBs.

Mr. BURGESS. It just struck me because that is not a normal course of events. You do a laparoscopy for pelvic pain diagnosis endometriosis. You are not necessarily going to be back in 20 weeks looking to see what things look like today, so that is a little bit of an unusual situation just from my recollection of clinical practice. I realize it has been a few years but that would be a deviation. Someone has to pay for it. Again, my concern there is if we involve the Medicaid system then again federal dollars are used in this test protocol so we can't really just say no federal funding was used so we can't be interested. I think we should be interested from a patient safety standpoint but there was a real possibility had this not been a fake study that federal funds might well have been used depending upon the part of the country where the study was conducted because obviously we heard on this committee time and time again about the greater and greater proportion of patients that are being covered by Medicare given the state of the—I am sorry, Medicaid, given the state of the economy.

Is there—I am not sure whether I need to address this to Dr. Menikoff or Dr. Less, but here you have albeit a make believe company and it got one positive response to several it sent out. Does anyone sort of take the 30,000 foot level look at this and say, wow, two IRBs turned this down and one bit? I wonder why it only had a 33 percent acceptance rate out there in the universe of IRBs. Would that trigger a red flag on anyone's part in any of the federal agencies that have oversight not necessarily of the federal funding but of the patient safety aspects?

Mr. DUEBER. Yes, I think it has a big bearing with all due respect. I sit here, you know, feeling troubled that only three were selected, and we were one of the three. I mean why not select 40 or 50 of them? I mean I understand where you are going, and I honestly have to say I am on your side. I want my company to do an excellent job of protecting human subjects, and of course we have work to do. We are not perfect. No one is perfect.

Mr. BURGESS. I am going to interrupt you in the interest of time because the chairman is going to cut me off. He always does and I can't stop him. But, Dr. Menikoff or Dr. Less, is there any mechanism in place right now when you only have a 33 percent uptake rate that that raises a red flag, that maybe this was a protocol that needs to be looked at more scrupulously?

Ms. LESS. Congressman, there is a check in place in our regulations that when a study for a medical device, when it is presented to an IRB, the IRB is supposed to make the determination of whether or not an IDE is needed. If the IRB disagrees with the sponsor who has presented it as a non-significant risk product, if the IRB decides it is not a non-significant and it is, in fact, significant risk, the IRB is supposed to tell the sponsor that and the sponsor is supposed to report it to FDA within 5 days. So there is that check in place. FDA would be notified if an IRB, as they were supposed to do, make a decision, and if they disagreed with the sponsor.

Mr. BURGESS. Did that happen in this make believe world that we are in today? Did any of that occur?

Ms. LESS. No, that did not occur.

Mr. BURGESS. I know I am a little slow on this, but who should have picked that up? Where should that have occurred?

Ms. LESS. Well, the sponsor, who was fake, should have been reporting that to FDA.

Mr. BURGESS. And does the FDA have any mechanism in place to know that, oh, my goodness, this sponsor did not make any sort of report at all. We wonder why. There is some curiosity to go back and look and see why no report was made.

Ms. LESS. We wouldn't necessarily know if the sponsor did not comply with the requirement and not make that report. We wouldn't necessarily know. If they did make the report then we would go out and look at the study, decide whether or not we agreed with the IRB or the sponsor, decide whether or not it did in fact need an IDE.

Mr. BURGESS. So there is no way to track, I will just call them dropped cases for want of a better word, if the investigations just don't come back to you, then you don't know why they weren't pursued?

Ms. LESS. Well, what could have actually happened if they were a real case if a sponsor goes to an IRB and says my product is low risk, the sponsor says, no, in fact, that is actually high risk, that sponsor then could not conduct the trial. They would make the report to us. They would not be able to start the trial. If they went—and so there is that check in place that they would be reporting to us and—

Mr. BURGESS. What is they were venue shopping on this and went to several IRBs simultaneously as the fake company did?

Ms. LESS. Well, hopefully when they went to the second IRB they wouldn't lie and say that it is still a low risk product. They would fix their protocol or go in and say this is a significant risk product because again that second IRB would have to ask the sponsor of the trial is this a significant risk, does it require an IDE? The product could not be shipped and the study couldn't be started without our approval too for this kind of product so there is that second check in place that the trial could never have gotten—or should never have gotten started without coming to FDA.

Mr. BURGESS. Mr. Kutz, was that your finding as well?

Mr. KUTZ. We said it was significant risk and for the one IRB we provided a 510(k) which would have been a prior marketing approval but, no, we said it was a significant risk. We did not say it was low risk.

Mr. BURGESS. So should the FDA have picked up on that fact and gotten back to you and said hold the phone?

Mr. KUTZ. We never contacted the FDA.

Mr. BURGESS. Oh, you did not?

Mr. KUTZ. No.

Mr. BURGESS. But in the real world it would be your obligation as an investigational company to contact the FDA?

Mr. KUTZ. I am not aware of the regulations on that.

Mr. BURGESS. Right, but it was GAO in charge of the fake company so you were CEO of a fake company. If you were a CEO of a real company, would that have been the obligation of the real company to do that?

Mr. KUTZ. FDA knows the—I don't know the answer to that.

Mr. BURGESS. I need a yes or no or the chairman is going to whack me.

Ms. LESS. Yes. The fake company should have reported to FDA that the product was determined to be a significant risk. These types of products, we have a guidance document that lists significant and non-significant risk products. This type of product is listed as significant risk.

Mr. BURGESS. It is voluntary at this point. No one is required to do that so if somebody slipping under the radar a time or two, we really got no way to go back and do any sort of internal check on that. I would be interested if I were the FDA today, are there any others that have slipped under our radar like this? How many other bad studies have we missed?

Ms. LESS. It is not voluntary. It is mandatory that the sponsor report to us within 5 days of the IRB tells them that a product that they presented to them is significant risk.

Mr. BURGESS. What penalty might they invoke if they don't report?

Ms. LESS. If they don't report, we would go after them. We could issue a warning letter. We would go out and inspect, issue a warning letter.

Mr. BURGESS. What if you found that federal funds were used such as in the Medicaid or S-CHIP system, would HHS become involved at that—

Mr. STUPAK. Last one now, Mr. Burgess. We have been more than generous with time. We have another member waiting.

Mr. BURGESS. All right. If the federal funds were used to pay for the surgeries or the procedures, Dr. Menikoff, would that get your interest?

Dr. MENIKOFF. When you are referring to federal funds being used, the general sense of that is basically that the funding for the study taking place, in other words, an investigation that is funded by NIH or CDC or FDA itself may be running a study. Normally probably the fact that one of the procedures is paid through Medicaid, for example, wouldn't implicate that. The key is that somebody in getting federal funds to run one of these studies, if this study was done with NIH money, GAO again didn't fully respond, but the odds are extraordinarily low that any of this could have happened because in getting those funds the legitimacy of this entity would have been vetted this way and that. You would have had top scientists asking who is this person? What knowledge does he have to do this? Is he a well-trained physician? What papers has he written?

Many, many parts of this system work together and particularly on the HHS funded side to make sure that we have legitimate things happening and this information then works together with the IRB in terms of making sure that there are substantial protections in place. So again the facts do speak for themselves. GAO didn't end up producing a fake, federally-funded study. I think it would have been very, very difficult to do that. There are many, many protections in place.

Mr. BURGESS. And yet still federal funds could have been put—

Mr. STUPAK. Mr. Burgess, I really do have to in all sincerity—Mr. Markey has been waiting patiently. You are more than 7 minutes over.

Mr. MARKEY. Thank you, Mr. Chairman, very much. Mr. Dueber, based on the review that your company conducted here, would you have been comfortable with your wife or your mother being treated in her abdomen with the solution your company approved?

Mr. DUEBER. I can't answer that. I do not know.

Mr. MARKEY. You don't know if you would be comfortable recommending to your wife and mother something that you recommended for all of these other—

Mr. DUEBER. You know, it is speculating. I would have to—you know, I don't know. The doctor that I talked to that was on our board that approved this does this surgery, uses a similar product. He felt it was safe. We have had it reviewed by an expert, outside expert, and he says it is safe. I mean the ingredients that supposedly were in it are supposed to be—the active ingredients are supposed to be safe. The inactive ingredients have no interference with the effectiveness of active ingredients so absent any other information to prove them wrong, I guess if I was in a decision-mak-

ing mode, I would probably say, yes, go ahead and use it on them. But of course that is their decision, not mine.

Mr. MARKEY. Well, if you look at your record the committee requested information on all of your reviews for the past 5 years, and this is what you provided, that your company reviewed a total of 356 proposals for human testing, and you approved all of them. So that means you approved 100 percent of all the studies that you reviewed.

Mr. DUEBER. I am not sure the numbers you are looking at, 356, what—

Mr. MARKEY. You approved—356 protocols were approved and the board voted—

Mr. DUEBER. For what time period? I am sorry.

Mr. MARKEY. Over a 5-year period.

Mr. DUEBER. No, we have approved more studies than that, sir.

Mr. MARKEY. These are the records that you submitted to the committee, and I am working off of your documents that you provided to us.

Mr. DUEBER. I believe you may be looking at the audit numbers that we sent to you.

Mr. MARKEY. We have every—you provided to us every vote which the board cast over the last 5 years, and of the 356 protocols you approved every single one of them, 7 to 0 on each vote, except on one occasion when 1 single board member dissented, so that means out of 2,492 votes cast by board members all but one were in favor of approval.

Mr. DUEBER. We have been requested to provide you with a list of all of our protocols since the inception of Coast and which ones were approved, which ones were not approved, and we will work on that and send that information to you. I can tell you that we do audit a fair number of protocols. In the last 3 years we have done about 50 to 60 audits, and some of those audits, we have overturned the original ruling of the original approval of those studies.

Mr. MARKEY. Mr. Kutz, let me read to you from their web site. Here is what it says. It says Coast IRB's quick document turnaround will save you valuable time and ensure that you can seamlessly move on to the next steps quickly and efficiently. Our superior service guarantees your site approval documents will be sent to you the next day following every board meeting. In this case, do you believe that emphasis on speed contributed to the company's failure to conduct even cursory due diligence which if it had been done by the firm would have been as a result of a basic documentation review found that there was ultimately a fictitious nature to this entire enterprise?

Mr. KUTZ. The answer is probably yes. One of the reasons we picked the three we picked were because they appeared to have the less stringent documentation requirements. That is why we picked them. So we were testing the system. We were picking ones that we thought would have the less stringent paperwork requirements. And, in fact, as I mentioned also, the other thing that this IRB was selected is because they offered us a coupon.

Mr. MARKEY. Well, I think that it is pretty clear that—I know Mr. Dueber doesn't see it that way at this particular point in time, but I think the GAO and this subcommittee are providing a real

service to your company, sir. I think that we are trying to help to protect against such a lackadaisical system harming human beings. And you seem to be outraged actually in our pointing out this deficiency in the way in which your company conducts business. I just think it is important for you, sir, to reconcile yourself to this as an intervention in underlying corporate pathology and that we are trying to help you correct your business practice so that the public is protected.

I know you don't see it that way right now, but I think when you look back years from now you will see it that way, and I just think that perhaps now you are being advised by counsel to take the position which you are taking in your testimony here today, but it is not helpful to you to be denying the obvious which the GAO and our subcommittee chairman have identified to you. That is my advice to you. Try to start out where you are going to be forced to wind up anyway. It is going to be a lot prettier. This testimony that you are delivering today is not helpful to yourself or to the cause of insuring that there are real processes that protect the public. Thank you, Mr. Chairman.

Mr. STUPAK. Thank you, Mr. Markey. A couple questions I want to ask to follow up Mr. Burgess, and I think Mr. Walden hit on it too. On IRB shopping, IRB shopping, this is a practice in which researchers shop their protocol around to different IRBs until they get an approval. In 2002 the previous administration considered issuing regulations to require researchers to disclose prior IRB decisions so people would know if the study had been rejected in the past. On January 17, 2006, the previous administration withdrew this proposal, concluding that IRB shopping does not occur or does not present a problem to an extent that would warrant rulemaking at this time, so 4 years later they withdraw it.

According to this decision, the administration apparently felt they had no reason to believe IRB shopping was occurring with any regularity. Dr. Less, that came out of the FDA. Who would have made that decision in the FDA? Would it have been the FDA, HHS, the administration, who would have made that decision to withdraw this form shopping—IRB shopping requirement?

Ms. LESS. Mr. Chairman, after we issued the Advance Notice of Proposed Rulemaking, we evaluated all of the comments received. We had a working group involving experts from across the agency including our Office of Chief Counsel, all of the centers, and we looked at the comments and made that decision based on the information that we received and also in light of current regulations and the protections that we think that our regulations offer.

Mr. STUPAK. So you asked IRBs and they said, no, we don't do that?

Ms. LESS. No. We put it out for public comment and we got 55 comments. We reviewed all of those very carefully. We looked back at the IG report, which said that they were aware of a few case of IRB shopping, and the comments that we received, we also didn't have any real reason to believe that there was any concern over IRB shopping. There are a number of reasons why companies will go to multiple IRBs for legitimate reasons. Sometimes a company will go to more than one IRB at the same time simply to get their study up and running more quickly.

That doesn't necessarily mean they are shopping for the fastest or the least stringent IRB. We also can—we were concerned with the burden that it would put on IRBs in the sense that if you had a study with multiple sites, say 10, 20, 40 sites, if all of those IRBs had to share previous reviews, we felt it could overwhelm the system. And without knowing the other IRBs review practices, you would have no basis for deciding on the merit of that review. And we have seen that as an instance with say adverse event reporting.

Mr. STUPAK. So when Mr. Dueber—let me ask you this. We asked you when you were interviewed last week by the committee staff, you disagreed. You said that IRB shopping, and I quote—in fact, if you want to look at your testimony it is front of Dr. Menikoff there on page 83, I believe it is. It has a green tab on it there. When asked about IRB shopping, you said, "Has been a problem of IRBs, I understand for quite some time." So IRB shopping is a concern then, right, amongst IRBs, that they are going to go get a bad decision from one IRB, so they go to another IRB until they get it, that is a problem?

Mr. DUEBER. From my perspective and my company's perspective, it is a problem and—

Mr. STUPAK. Then answer me this. This is your coupon that you gave out to Mr. Kutz. On the bottom of the coupon it says, and I am going to read directly now, it says Coast IRB's free test drive offer applies towards initial protocol informed consent form and investigator's drug brochure reviews only, \$1,300 value. Coast IRB, LLC pledges to protect the full confidentiality of all research studies sent to us for review. In 2005, the FDA removed the guidance prohibiting IRB shopping. As such, you are free to use our free test drive offer to compare Coast services with another IRB's concurrently if after comparing our services to those of another IRB, you choose not to continue with Coast IRB, we will destroy all documentation we have on file associated with your study.

Neither your money, research time or confidentiality will ever be at risk. It sounds like to me you are encouraging with this free coupon IRB shopping, the practice that you say you are against.

Mr. DUEBER. Sir, that marketing piece was created before I arrived at Coast, and we are no longer using that for that particular reason. But, you know, our position is that—and the company's position has been that IRB shopping is a problem, and there needs to be some kind of a database that everyone can refer to to see if someone has submitted—a sponsor has submitted a protocol to some IRB and other IRBs can check that before we approve a study because—

Mr. STUPAK. Do you think there should be a ban on IRB shopping, and if a stud is rejected should be sent to the FDA?

Mr. DUEBER. I think the last part probably, yes, but we are in favor of improving the system and making it more difficult for people to do that because obviously that is not healthy.

Mr. STUPAK. Right. Mr. Kutz, under current law if you had been a real company, you would have been allowed to ignore these two rejections you received and continue with your approval from Coast, isn't that right?

Mr. KUTZ. I believe so, and actually one thing I would mention on the shopping in our initial e-mails to the IRBs we sent this to, we said very specifically that we were shopping for an IRB.

Mr. STUPAK. OK. So they all knew you were shopping, you were IRB shopping?

Mr. KUTZ. That is what our e-mail said, yes, the e-mails from the requests you got from the IRBs.

Mr. STUPAK. OK. And after you got the approval from Coast, could you have begun your experimental testing on human beings? Would there have been any other steps in the FDA or HHS review before you started your experimental test on real people and putting this fluid here, our liter bottle of Adhesiabloc in the pelvic abdominal cavity of women?

Mr. KUTZ. As I mentioned, because there is no federal dollars associated with it, my understanding is yes.

Mr. STUPAK. Thank you. Mr. Burgess, I know you always have questions.

Ms. LESS. Mr. Chairman, if I could clarify.

Mr. STUPAK. Sure.

Ms. LESS. That study should not have been started. It was a significant risk product. It would have required approval from FDA so the sponsor should never have started the study without coming to FDA.

Mr. STUPAK. Who should have come to FDA?

Ms. LESS. The sponsor. The sponsor would go to the IRB, get IRB approval, and they also would be required to get FDA approval before that study could start and before any product could be shipped, so the sponsor—

Mr. STUPAK. What is the requirement to do that?

Ms. LESS. Pardon me?

Mr. STUPAK. What was the requirement to do that? I got my protocol approved. I got my consent form approved. So why would I have to go to the FDA?

Ms. LESS. Under the IDE regulations and investigational device exemption regulations at 21 CFR part 812 for a significant risk product, which this is, the sponsor would be required to get both FDA and IRB approval before it ships the product or starts the trial.

Mr. STUPAK. That is because Mr. Kutz misrepresented, but what if it was some other project already approved? There was no requirement to go to the FDA because we had what, a 510(k) there, right?

Mr. KUTZ. We faked the 510(k).

Mr. STUPAK. We had a 510(k) so we don't have to go to the FDA on this one. He could have started on real patients if it was a real one.

Ms. LESS. Well, hopefully the sponsor, if it was a real sponsor, would have understood that this product is not subject to 510(k).

Mr. STUPAK. And what do you do to make sure a real sponsor does that?

Ms. LESS. A real sponsor is supposed to come to FDA—

Mr. STUPAK. I know. There is a lot of assumption in these laws, aren't there, that people are being above board. We proved today they are not.

Ms. LESS. Actually we have a number of programs in place where sponsors can come to FDA, ask if they need an IDE. We have a pre-IDE process where they can submit a pre-IDE to us, have us look at the protocol, look at the device, look at the testing that they have done to see whether or not it needs an IDE.

Mr. STUPAK. With all due respect, FDA hasn't been doing their job. That is why we are having this hearing because when we did Copernicus study 3014 which there was criminal fraud and your own CID asked FDA to do criminal charges against Copernicus and the doctors who were doing this, FDA refused to do it. You rejected it. So there is very little faith on this side of the dais that FDA is doing it right. So when we suppose people are going to do it and we suppose the FDA is going to do their job, we know what the end results are. Unfortunately, people die. I will go to Mr. Burgess.

Mr. BURGESS. Mr. Kutz, let me just ask you, my understanding is you based this fictitious product on another product that actually existed but didn't have a good track record, is that correct?

Mr. KUTZ. We got it on the Internet off of FDA's web site and then we substantially altered the entire—we had a format. We didn't know what a protocol actually was supposed to look like so we got one just so we could know what it looked like, and then we changed it completely and then we actually made up the ingredients.

Mr. BURGESS. How many FDA protocols did you have to look at before you found one that struck you as a good one to proceed?

Mr. KUTZ. We just wanted one. I don't know if there were any more or not. We just found one on the Internet and once we found that, we just used the format. We didn't use the actual details of it. We created our own. It just showed us what one looked like.

Mr. BURGESS. Was it hard to find one that led you in the right direction?

Mr. KUTZ. Yes. I don't think there were a lot of them out there.

Mr. BURGESS. OK. Dr. Less, Dr. Menikoff, I am assuming that the Inspector General at HHS has been notified of this situation, is that correct? I mean does HHS have—

Dr. MENIKOFF. No. We referred this to FDA's investigators.

Mr. BURGESS. OK.

Dr. MENIKOFF. That is the letter we sent.

Mr. BURGESS. Will it at some point go to HHS IG?

Dr. MENIKOFF. No, we plan to refer it to the FDA and we talked to the investigators that work under Dr. Less.

Mr. BURGESS. Had there been Medicaid funds used on any patient who received this compound inappropriately, would that have triggered HHS' involvement?

Dr. MENIKOFF. I don't believe so. Again, the HHS jurisdiction that OHRP has relates to there being a funding agency for the study so basically NIH or CDC—

Mr. BURGESS. Or CMS?

Dr. MENIKOFF. Excuse me?

Mr. BURGESS. Or CMS?

Dr. MENIKOFF. CMS could act as a funding agency for the study. The fact that one patient in the study got paid and—

Mr. BURGESS. We heard testimony by Mr. Dueber that the funding for the study was going to come from the third party coverage

of the patient essentially. Perhaps there was no charge for the study protocol or the protocol drug but there is a substantial amount of activity that has to occur to get to the place where the drug is administered and all of that activity was presumably going to be paid for by a third party payer, so in a way CMS would have been funding this study had it proceeded if Medicaid patients had been enrolled or S-CHIP patients.

Dr. MENIKOFF. My understanding is that is not the way in which something becomes HHS funded in terms of OHRP's jurisdiction. The basic issue is has somebody applied for a grant from an HHS grant making agency and they then approve this. I mean that is the protection, and it is actually a very strong protection. Again, this would not have happened if somebody tried to get HHS funding. I think it is extraordinarily unlikely, and people who are enrolling in HHS funding studies should actually be relatively confident that—

Mr. BURGESS. This whole deal is extremely unlikely and yet we find ourselves here in a parallel universe that the GAO made for us, and now we are having to try to pick our way through it. I just find it—I personally find it unbelievable that HHS is not more interested in the fact that funding sources could have been diverted into a bogus study and the patient required to have a second procedure, a second look procedure, 20 weeks later. I mean this is a big dollar item that we are talking about, 50 patients receiving a second look laparoscopy. There is no way to know how many of those would have been Medicaid, but that is a significant expenditure.

Dr. MENIKOFF. Congressman, it sounds as if you are talking about use of federal funds for an inappropriate purpose, that is—I don't know what unit of HHS would deal with that basically. OHRP is dealing with the human subjects protection aspect of it, not misappropriation of federal funds or misuse of federal funds in some way. I can't comment on what part of HHS does deal with that.

Mr. BURGESS. Well, give us some comfort. Now what are the next steps that are going to be taken here? Clearly, there are things that need to be improved but are there some enforcement steps that are going to be taken? What happens next?

Mr. KUTZ. Only with respect to the one referral. I think the bigger picture is that you had the set of protocols that went to three IRBs and you get two completely different answers at the same time. That is the part I think that should concern the subcommittee here. On the one hand, two IRBs said this was a ridiculous protocol, unsafe to patients. It should have never been approved. Another one is still testifying as we speak that it was perfectly safe. It is hard to believe you could have that divergent of a situation and that raises questions to me about the whole IRB system, especially the private IRB system.

Mr. BURGESS. And, Dr. Less, would you concur that from FDA's perspective that there is reason to be concerned about the whole system?

Ms. LESS. No, sir, I would not. I think under this circumstance from what I have heard this product was a significant risk product. It should have been submitted to FDA for review. The study would not start without FDA and IRB review, and in this case there

would have been that safeguard in place with having both the IRB approval and FDA approval needed before any patients could be put at risk or the study could have even started.

Mr. BURGESS. So any enforcement activity would be directed toward a company that doesn't exist that was made up by the GAO, would any enforcement activity be directed in Coast's direction for proceeding with a study with tenuous underpinnings?

Ms. LESS. Without seeing the report, I can't comment on that but in general FDA has taken action when an IRB has failed to make the determinations that it is supposed to make meaning they found significant risk determinations and looking to see whether an IDE is required for the study.

Mr. BURGESS. OK. Well, so what would happen? What would that action be?

Ms. LESS. We would go out and do an inspection of the IRB, look at their studies, their processes, see whether there were other studies that perhaps a wrong decision was made and if we found a problem, we would issue a warning letter. We could impose sanctions. And then we would see if they put a corrective plan in place to take care of that. If not, then we could pursue other activities.

Mr. BURGESS. Do you ever make a silent pact with yourself that we will never use this IRB again? Do you keep a list? Is there a watch list?

Ms. LESS. Well there is a—all of our warning letters are public. They are on the web site so any sponsor doing a study should be looking at that web site to see—

Mr. BURGESS. Is there any way to know that one side is talking to the other on this because this seems to be one of the problems we have encountered today. You had to say this was a bad deal, one said it is OK. Nobody talks about it, so it potentially could have gone forward with a very, very difficult study from the standpoint of a patient.

Ms. LESS. Well, warning letters are public. IRBs are obviously not happy to receive those. They take them very seriously and do some corrective actions. We require that they submit a corrective action plan within 15 days if we issue a warning letter, and we do follow up to make sure that those corrective actions are taken.

Mr. BURGESS. Well, now Coast had on its web site Q and A, have you ever been investigated from the FDA, and they said, well, they had but they got a commendation, but in fact that wasn't accurate, I understand now, is that correct?

Ms. LESS. I have not seen the information on their web site. I am sorry, Congressman.

Mr. BURGESS. This is again a printout of Coast's web site. Do we have that to project? The frequently asked questions—

Mr. STUPAK. Coast's web site, do you have it? No, they don't.

Mr. BURGESS. Under the frequently asked questions section, have you ever been audited by the FDA? Answer, December 15–17, 2003, Coast IRB was selected for a routine surveillance inspection. We received a commendation from the FDA investigator regarding the thorough and effective oversight provided by our IRB operations. A follow-up audit was conducted in 2005 at which time no further action was required by the FDA investigator. Do you think that is a true statement?

Ms. LESS. We inspected Coast four times. The first three times we did issue letters saying that voluntary action was indicated, meaning that we found minor deviations from the regulations and we asked them to—in the letter we pointed out what those deviations were, pointed them to the appropriate regulation or guidance. They did submit a letter back to us stating that they had taken care of the issues that we addressed in each of those three letters.

Mr. BURGESS. Were those warning letters? Would those be the equivalent of warning letters?

Ms. LESS. No, they did not rise to the level of a warning letter. They were what we call voluntary action indicated. We have no action indicated, voluntary action, and then official action, which is the warning letter level.

Mr. BURGESS. Have they ever received a warning letter?

Ms. LESS. Yes. Their most recent inspection that we conducted in 2007, we issued a warning letter to the IRB.

Mr. BURGESS. And we had this approval in October, 2008 by the board so presumably they were under a warning when this study, proposed study, was to be undertaken, is that correct?

Ms. LESS. We had issued a warning letter, and they submitted a corrective action plan, told us that they had put training in place for their staff and were testing their staff on the conduct under the regulations of what would be required, and so we had reviewed all of that information. They had also, I believe, hired an outside consultant that was also supposed to be overlooking their processes.

Mr. BURGESS. Is that the basis on which you gave them a commendation?

Ms. LESS. We don't give commendations to anyone, Congressman.

Mr. DUEBER. In addition to that, Congressman, we—

Mr. BURGESS. But that is misleading statement on your web site then, isn't it? She said the FDA doesn't give commendations.

Mr. DUEBER. They sent us a letter reinstating our use of expedited review. We had given them a corrective action plan and acted very swiftly. In addition to that, our CEO—

Mr. BURGESS. OK. I am going to interrupt you because I am going to get cut off again. If you would be good enough to provide that letter to the committee, we would very much like to—

Mr. DUEBER. The committee already has that letter. We provided that in the package of materials we sent.

Mr. BURGESS. Thank you, Mr. Chairman. I will yield back in the interest of time.

Mr. STUPAK. Thank you, Mr. Burgess. Dr. Less, you said earlier that warning letters are more serious violations. In fact, the FDA issued a violation letter—a warning letter, excuse me, a warning letter on March 11, 2008, to Coast for three different parts on expedited review of IRBs, isn't that correct?

Ms. LESS. Yes, sir, that is correct.

Mr. STUPAK. And now Mr. Kutz has sent a letter about this situation and how Coast had reviewed this IRB—or this protocol, so will the FDA now invoke a more severe penalty than on Coast based—they already have a warning letter sitting there in their file. Now they got another allegation of wrongdoing. What will the FDA action be?

Ms. LESS. Congressman, we will need to take all that information into account and do a thorough evaluation. Normally, if we issue one warning letter, the next warning letter would include sanctions and we would take more serious action, but without knowing the specifics and having reviewed the entire case, I can't comment on this particular one.

Mr. STUPAK. Mr. Dueber, let me ask you this, and I will wrap up this hearing here. Are all of the seven people who approved this protocol, the bogus protocol, do they still work for Coast?

Mr. DUEBER. Yes, they do.

Mr. STUPAK. OK. Has anyone at Coast lost their job because of their failure to adequately review this protocol?

Mr. DUEBER. One individual is leaving the company shortly.

Mr. STUPAK. But not as discipline action for this matter?

Mr. DUEBER. No, sir.

Mr. STUPAK. OK. And how about the chair of the Institutional Review Board here, your chair of this board that reviewed this protocol. She indicated she didn't even read the protocol. Is she still working for you and she is still a member of the company?

Mr. DUEBER. Yes, she is. We evaluate our board members once a year.

Mr. STUPAK. OK. You said a couple times that you have changed your SOP. I take it that is standard operating procedure review process, right?

Mr. DUEBER. Right.

Mr. STUPAK. So it sounds like a lot of good changes have been implemented.

Mr. DUEBER. Yes, that is correct.

Mr. STUPAK. So a lot of good actually has come from being caught here on this bogus—

Mr. DUEBER. Yes, it has, and I might add that during our lunch break I talked to Dr. Less and I basically pleaded with her to bring FDA into my company and do a full top down, you know, front to back audit of our company because since I started with the company, I have done nothing but try to make sure that the company does exactly what it should be doing and do the best it can of any IRB.

Mr. STUPAK. And in all fairness, you have been there since December of 2008, right, basically 4 or 5 months?

Mr. DUEBER. I started at the end of September.

Mr. STUPAK. September.

Mr. DUEBER. And, you know, my track record is totally opposite of what we are talking about here so I need time to improve things, and we are improving. We have done—we have got an incredibly dedicated staff more so than I have ever seen in any company I have worked for before that they really—everyone, their first thing that they worry about is protection of human subjects.

Mr. STUPAK. Then how did they miss this one so bad? I guess that is the part that baffles us.

Mr. DUEBER. Well, we got hoodwinked. I mean, you know, this was a pretty good—

Mr. STUPAK. You didn't get hoodwinked. You took the bait hook, line and sinker. I mean in your testimony in all fairness you said that once you got the letter you started looking at it. It took sec-

onds to figure out that something was wrong here. I think it was the doctor's credentialing that was 19 years old. It took you seconds to do that just by going on the Internet. The procedure that we used, our magic elixir here, was actually found on the Internet. All this could have been discovered with a little due diligence. Hopefully, I am glad to hear some good things have come from all this whole thing also.

Mr. DUEBER. Definitely.

Mr. STUPAK. I want to thank you all for coming here and thank you for your testimony today. That concludes all questioning. I want to thank all of our witnesses for coming. The rules of the committee provide that members have 10 days to submit additional questions for the record. I am sure there will be some. I ask unanimous consent that the contents of our document binder on the desk there be entered in the record provided that the committee staff may redact any information that is business proprietary, relates to privacy concerns or law enforcement sensitive. Without objection, the documents will be entered into the record.

[The information appears at the conclusion of the hearing.]

Mr. STUPAK. This concludes our hearing. The meeting of the subcommittee is adjourned.

[Whereupon, at 1:55 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

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2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115

MANUSCRIPT (202) 225-2927
FACSIMILE (202) 225-2523
TELEPHONE (202) 225-3641

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Opening Statement of Rep. Henry A. Waxman
Chairman, Committee on Energy and Commerce
Institutional Review Boards that Oversee Experimental Human Testing for Profit
Subcommittee on Oversight and Investigations
March 26, 2009

Thank you, Chairman Stupak, for calling today's important hearing on the role of Institutional Review Boards in protecting the health of men, women, and children who participate in experimental biomedical testing.

New drug protocols, innovative surgeries, and high tech medical devices have the potential to revolutionize the health of our citizenry and extend the lives of all Americans. But we have to make sure that any experimental techniques are examined very closely before they are actually performed on people. We have to ensure that both researchers and their subjects understand the real risks. The question for today's hearing is whether this is happening.

Last year, the Committee asked the Government Accountability Office to investigate whether IRBs were rubber stamping experimental research protocols in order to collect fees. Many IRBs are for-profit entities that have been increasing their revenues over the past several years. The Committee also asked GAO to investigate whether protocol sponsors were engaging in IRB shopping, basically going from one IRB to another until a protocol is approved.

Today we will hear the results of GAO's investigation. GAO invented a fake company, developed a fake protocol, and got it approved by a real IRB.

It is important to understand exactly what GAO was proposing to do. GAO's protocol would have been used on women undergoing invasive abdominal surgery. One of the dangers after this type of surgery is that when internal organs begin to heal, they develop scar tissue. If organs attach to each other or to other body parts, they can begin to malfunction.

According to GAO's protocol, at the end of this surgery, researchers would have poured a full liter of an experimental fluid inside a woman's abdominal cavity. The idea was that maybe this could prevent organs from attaching to each other. But GAO made up studies that did not exist, falsified the credentials of its doctors, and had absolutely no idea what the real-life implications of its proposal would be.

The company that approved this protocol, Coast IRB, will testify today about how this could have happened.

One thing we know about Coast is that they aggressively marketed their services. When GAO was considering whether to submit its fake protocol to Coast, the company actively solicited the business, even sending a coupon to GAO. Here is what it says: "Take us for a free test drive!" Then it says, "Coupon good for a one time research protocol review worth \$1300." And then it says, "Coast through your next study."

This is actually a coupon for experimental testing on human beings. The company virtually guarantees approval, and it offers the first review for free. Can you imagine going to the hospital for major invasive surgery and having your doctor ask whether he can use a device approved after cashing in a coupon?

In order to determine whether Coast was making good on its promises for quick and easy approvals, the Committee sent its own document request seeking "a list of all research protocols submitted over the past five years," including each protocol's sponsor and the final vote counts of board members either denying or granting approval.

Here is the information Coast provided to the Committee. Over the past five years, Coast's board has reviewed a total of 356 proposals for human testing, and it approved all of them. That means it approved 100% of the studies it reviewed. Of the 356 protocols approved, Coast's board almost always voted unanimously in favor of approval, usually by a vote of 7 to 0. There was only one exception, when a single board member dissented on just one occasion.

Over this same timeframe, Coast's revenues have more than doubled, increasing from \$4.4 million in 2005 to more than \$9.3 million in 2008. While this may be lucrative for Coast, it raises serious concerns about the safety of hundreds of experimental tests the company approved and the health of potentially thousands of people who may have participated in them.

We will have difficult questions for our witnesses today, and even though the answers may be unsatisfactory, this Committee will continue to push for reforms that will protect the health and safety of the American people.

**Committee on Energy and Commerce
Subcommittee on Oversight and Investigations**

Hearing Binder

DOCUMENTS FOR USE AT HEARING

Device Med-Systems (GAO)

1. Device Med-Systems (GAO) Protocol submitted to Coast IRB, Fox IRB and Argus IRB
2. "Jonathan Q. Kruger" Virginia Medical License

Coast Independent Review Board

3. Coast IRB Site Application Checklist (Oct. 30, 2008)
4. Coast IRB Board Meeting Minutes (Oct. 30, 2008)
5. E-mail chain between Denise Strasser, Adam Dodd, Melissa Cortes, and Christy Gorey (Oct. 30, 2008)
6. Informed Consent Form approved by Coast IRB (Nov. 6, 2008)
7. E-mail from Lisa Bean, Customer Relationship Specialist, to "Paul Jennings" (Jan. 13, 2009)
8. E-mail chain between Dan Dueber and Jonathan Emord (Mar. 6, 2009)
9. Coast IRB press release (March 10, 2009)

Argus Independent Review Board

10. E-mail from Valerie Golembiewski to "Paul Jennings" with attachment (Nov. 3, 2008)

Department of Health and Human Services- Office for Human Research Protections

11. E-mail regarding "IRB shopping" (June 3, 2003)
12. Compilation of Data about IRBs by HHS-Office for Human Research Protections (OHRP)

Food and Drug Administration

13. Withdrawal of Advanced Notice of Proposed Rulemaking on "Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews" (Jan. 17, 2006)

Additional Documents

14. Coast IRB Revenue: 2005-2008
15. OHRP Registration of Fake GAO Entities
 - Device Med-Systems (FWA)
 - E-Z Reviews, INC. (IRB Registration)
 - Maryland Hause IRB (IRB Registration)

Phake Medical Devices, INC. (FWA)

16. E-mail chain between Dan Dueber, Diane Marrow, Jonathan Emord and Andrea Ferrenz (March 17, 2009)
17. FDA Regulation, "Basic Elements of Informed Consent"
18. Letter from FDA to Darren McDaniel (Mar. 11, 2008)

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Clifton, Virginia 20124*

SUBMITTED BY:

Mark Bradshaw, MD
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Jonathan Q. Kruger, MD
*Principal Investigator
Device Med-Systems*

Signature

Date

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1 Background

An adhesion is defined as abnormal binding of adjacent fibrous tissue surfaces. Adhesions formed at sites which had no pre-existing adhesions are called "*de novo* adhesion". These include adhesions formed at sites traumatized after surgical procedures (surgical site *de novo* adhesions) and at sites which had no surgical intervention (non-surgical *de novo* adhesion). Adhesions reformed at sites which had pre-existing adhesion but are lysed are called "reformed adhesions". *De novo* adhesion and reformed adhesions can be further classified depending on the extent and severity of the adhesion at particular sites. Peritoneal adhesions, a frequent complication which are formed or reformed following abdominal surgery, can cause clinical symptoms including, but not limited to, abdominal discomfort, chronic pelvic pain, bowel obstruction and infertility in women.

Corrective surgeries are often needed to resolve adhesion-related complications. Preventive measures are therefore of considerable clinical importance. Increased awareness of peritoneal adhesions has encouraged the use of surgical techniques such as laparoscopy, designed to minimize peritoneal trauma. Also, numerous potential adjuncts are intended to separate peritoneal surface during post-surgical healing in order to prevent or reduce adhesion formation. Saline peritoneal lavage, antibiotic therapy and HYSKON® are the most common examples, but clinical experience with these treatments has been equivocal. FDA-approved INTERCEED® (TC7) Absorbable Adhesion Barrier (Gynecare, Somerville, NJ), Preclude® (Gore-Tex, Flagstaff, AZ) and Seprafilm® Bioabsorbable membrane (Genzyme, Cambridge, MA) has been proven efficacious, but as is inherent with barrier fabric or film products, the effect is localized and therefore site specific, requiring the surgeon to predict where adhesion would most likely form. Interest therefore continues in the development of an intraperitoneal device which functions more broadly as a post-surgical adhesion prophylactic.

Propylene Glycol, known also by the systematic name propane-1, 2-diol, is an organic compound (a diol alcohol), containing two hydroxyl groups (-OH groups) attached to adjacent by vicinal diols. It is produced by hydration of optically pure propylene oxide and fully miscible with water. Propylene Glycol has been shown to significantly reduce adhesion formation in animal models by means of hydro floatation and is believed to function through a physical effect by providing a viscous, lubricious coating on the peritoneal surfaces. In clinical evaluations conducted by Device Med-Systems, Propylene Glycol is found to be safe and marginally effective, with the greatest effect coming from a reduction in *de novo* adhesions. However, these solutions are rapidly absorbed from peritoneal cavity, allowing for an extended period of time for adhesion formation.

2.5 % ADHESIABLOC® Gel, Propylene Glycol and Isoleucine crosslinked by the addition of a sodium chloride, is a colorless, viscous aqueous solution formulated to a specific viscosity range. Crosslinking among the hydroxyl groups on the Propylene Glycol, the divalent sodium (Na^{+2}) and hydrocarbon groups on the Isoleucine is ionic in nature, resulting in a significant increase in solution viscosity compared to the starting

Propylene Glycol solution. The ionically crosslinked 2.5% ADHESIABLOC® Gel has shown to prevent or reduce adhesion formation by hydro floatation is as effective as the starting solution in preclinical animal models. Moreover, 2.5% ADHESIABLOC® Gel showed prolonged intraperitoneal residence time of at least 15 days, which is enough time for peritoneal healing. It is packaged in 250 mL Type I borosilicate transparent vials with 25 mm flip tear-off seals, and is a sterile, non-pyrogenic gel of a highly purified light molecular weight amino-diol alcohol adjusted to isotonicity with sodium chloride.

2 Objective

The objective of this single center pilot study is to demonstrate whether the investigative study device, 2.5% ADHESIABLOC® Gel is as safe and efficacious as, or superior to the routine Ringer's Lactated Saline control in preventing or reducing adhesions in patients undergoing peritoneal cavity surgery.

3 Study Enrollment

3.1 Inclusion Criteria

1. female patients aged over 18
2. patients undergoing peritoneal cavity surgery via laparotomy due to infertility, pain, and/or irregular vaginal bleeding with preservation of fertility
3. patients who are able to participate in the Week 1 - 4 post-surgical laboratory determinations
4. patients who will be required to schedule for a second-look laparoscopy as part of their treatment
5. patients agreeing on written, witnessed informed consent to participate in the study prior to any study-mandated determinations or procedures to be performed with the exception of the physical examinations as discussed on page 6

3.2 Exclusion Criteria (Pre-operative or Intra-operative)

1. patients in pregnancy (including ectopic pregnancy) or lactation period
2. patients undergoing tubal sterilization, reversal of sterilization, or tubal implantation during the surgical procedure
3. patients receiving cancer therapy including drugs and radiation within the last 3 weeks from the surgery
4. patients with lymphatic ($WBC \geq 12 \text{ K/mm}^3$), hematologic or coagulation disorders ($HGB \leq 8.5 \text{ g/dL}$), or taking anticoagulants
5. patients who have a history of hemochromatosis
6. patients who have hepatic ($AST \geq 50 \text{ U/L}$ or $ALT \geq 50 \text{ U/L}$) or renal ($BUN \geq 25 \text{ mg/dL}$ or $Creatinine \geq 1.5 \text{ mg/dL}$) disorders

7. patients taking oral or parenteral hypoglycemic agents for diabetes
8. patients whose pre-operative laboratory values are outside 20% of the normal range and considered clinically significant
9. patients who are immunocomprised or have autoimmune disorders
10. patients who are unsuitable for processing large fluid loads, such as patients with congestive heart failure
11. patients receiving any other peritoneal instillate containing corticosteroids, NSAID's, or HYSKON® (Dextran) (During the procedure, irrigants which may or may not contain heparin and/or antibiotics may be used if completely aspirated.)
12. patients in whom any other absorbable hemostat is left in the abdominal cavity (Surgicel® Avitene®, Gelfoam®, etc.)
13. patients receiving any other adhesion prevention adjuvant (INTERCEED® (TC7) Absorbable Adhesion Barrier, GoreTex®, Seprafilm® Bioabsorbable Membrane)
14. patients who will require post-surgical hydrotubation
15. patients with active pelvic or abdominal infection
16. patients who will undergo peritoneal grafting as part of their operative procedure
17. any surgical procedure at the time of the initial laparotomy that involves opening of the gastrointestinal or urinary tract
18. patients with 12 or more of the 24 anatomical sites contained adhesions as noted during the initial operative procedure (refer to Appendix I for list of the 24 anatomical sites)
19. patients who will have one or more of their anatomical sites removed during the initial operative procedure (refer to Appendix I for list of the 24 anatomical sites)

3.3 Duration of Study

The study duration is scheduled up to 20 weeks, from the first surgical procedure to the second-look laparoscopy (maximum not to exceed 24 weeks). Total enrollment is projected to take eight months.

4 Study Design

4.1 Design Consideration

A single (1) center will participate in this third-party blinded, parallel group, randomized and controlled study. A maximum of seventy (70) patients will be asked to participate,

but no more than fifty (50) patients, including those who are not evaluable, will be entered into the study. An evaluable subject, defined as one who has completed her scheduled second-look laparoscopy targeted for six (6) to twenty (20) weeks from the initial surgical procedure (minimum of six (6) weeks, maximum not to exceed twenty-four (24) weeks), are targeted total of forty (40), or 20 per group. These evaluable subjects will undergo peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy.

At the initial laparotomy, adhesiolysis, myomectomy, ovarian cystectomy, Fallopian tube repair, surgical treatment of endometriosis, ovulation enhancing surgical procedures, or other pelvic reconstructive surgical procedures will be performed. Subjects will be administered 1000 mL of 2.5% ADHESIABLOC® Gel or Ringer's Lactated Saline as an intraperitoneal instillate by a surgical assistant (third party) after the surgeon has completed the primary laparoscopy procedure, achieved complete hemostasis, aspirated all irrigants, removed all packs and sponges, and has left the operating area. Second-look laparoscopy will be carried out at the appropriate time interval. Instillation of solution by surgical assistant or third party is to maintain the blind study.

Safety assessment will be based on the preparative and post-surgical laboratory test values, concomitant medications and conditions, frequency and severity of adverse events, and overall evaluation at second-look laparoscopy.

The primary efficacy variable will be a total adhesion score using the modified American Fertility Society (mAFS) Scoring System applied to 24 anatomical sites. Scores from all potential adhesion sites will be averaged (divided into 24) to yield a total adhesion score, ranging from 0 to 16. Adhesions will be characterized as either *de novo* or *reformed* depending on their characteristics and classifications. Sites with *de novo* adhesions will also be further classified as surgical versus non-surgical.

The secondary efficacy variable will be proportion of sites with adhesions, a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. As above, adhesions will be characterized as *de novo* versus reformed and surgical versus non-surgical. Additional secondary variables will include the extent and severity of all categories of adhesions.

In addition, adhesion sites will be organized by the presence or absence of endometriosis, use of sutures, and the method of adhesiolysis (sharp dissection; laser).

4.2 Study Procedure

Each patient asked to participate in the study will be assigned sequentially, by means of a random number scheme, to one (1) of two (2) following groups:

1. A study device group: 2.5% ADHESIABLOC® Gel, or
2. A control solution group: Ringer's Lactated Saline (RLS)

Case Report Forms (CRF) for the evaluations presented in Appendix II will be provided in individual binders, one set per patient, for recording purposes with exceptions of Concomitant Medication and Adverse Events. These exceptions will be further discussed in 4.2.7.

Patients participating in the study will undergo the following evaluations and procedures:

4.2.1 Preparative Procedures (VISIT 1)

Within the three (3) weeks prior to the initial surgical procedure, patient's general background information such as past surgical history, current medications (prescription, non-prescription, and iron supplements) and checklists for inclusion/exclusion including informed consent will be obtained and recorded on the CRF.

Each patient will undergo physical examination including vital sign (temperature, weight and height, respiration rate, blood pressure and pulse) measurement. Since these physical examinations are a standard pre-operative practice, they may be performed prior to the patient's signing of the consent form as long as the examinations are performed within the three (3) weeks prior to the initial surgical procedure. The results will be recorded on the CRF.

Also, each patient will perform the below-listed laboratory tests within the three (3) weeks before the initial surgical procedure. These test results will be used as a baseline for evaluating the safety of intraperitoneal instillation of the study solution:

1. Hematology (CBC)
2. Serum electrolytes (sodium, potassium, calcium, chloride)
3. Blood Chemistries: BUN, creatinine, albumin, total protein, total bilirubin, phosphorus, SGPT, SGOT, alkaline phosphatase, and uric acid.
4. Urinalysis, including a human chorionic gonadotropin (hCG) urine pregnancy test

The investigator will review the laboratory data and record the information on the CRF. All values should be within 20% of the normal range. If any values are outside of 20% of the normal range, the investigator will consider whether the value is clinically significant and provide comments on the CRF regarding their decision to include or exclude the patient. The principal investigator will review and sign on the CRF after carefully examining and verifying all of the entries in this section.

4.2.2 Initial-Operative Procedures (VISIT 2.1)

The patient will be assigned the next available study number four (4) hours prior to the scheduled surgery. The investigator will assess the existence of any adhesion at each of the 24 anatomical sites listed in Appendix I prior to any adhesiolysis.

If an adhesion is present, this information will be recorded on the CRF. If an adhesion is fully lysed, this information will also be recorded on the CRF by answering YES to the lysing question for each anatomical sites, along with the method of adhesiolysis (sharp

dissection, cautery, laser). The severity and extent of the adhesion(s) will be characterized as shown in Appendix I.

The presence of endometriosis and whether the tissue was excised or fulgurated will be assessed at each of the 24 anatomical sites. The investigator will also note suture use and any other surgical intervention for each of the 24 anatomical sites on the CRF. The type(s) of sutures used will be noted along with a synopsis of the procedure(s) on the CRF.

The investigator will also provide data regarding the following:

- an account of the actual surgical procedures (*e.g.*, cystectomy, myomectomy, *etc.*) rendered
- estimate of total operative time of these procedures
- estimate of blood loss (in mL/cc) due to these procedures
- all concomitant medications used
- the stage of endometriosis (if present) utilizing the MAFS scoring system

All pre-existing adhesions will be drawn at the time of the surgical procedure, or shortly thereafter within 36 hours. Careful attention needs to be paid clearly identifying the anatomical site, extent, and severity of each adhesion. Any adhesions not lysed will be recorded on the CRF. All incision lines will also be recorded on the appropriate diagrams. An optional worksheet will be provided as an aide for recording this adhesion assessment.

The study device or control solution, as determined by the blinded randomization schedule, will be administered into the peritoneal cavity by the surgical assistant after the surgeon has completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs and sponges, providing the intraoperative exclusions criteria do not apply. The Principal Investigator will identify the surgical assistant on the CRF.

4.2.3 Initial Post-Surgical Procedures (VISIT 2.2)

The patient will be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. The result will be recorded on the CRF. Any adverse experiences noted by the patient and/or observed by the staff, *i.e.*, post-surgical pain, nausea, infection, and *etc.*, also will be recorded on the CRF. Serum electrolytes, hematology (CBC with differential) and blood chemistries will again be conducted prior to the patient's discharge from the hospital or within 4 days of the initial surgery, whichever comes first. The date of discharge will also be noted.

Additional comments may be made on the CRF. The principal investigator will review and sign the CRF after carefully examining and verifying all of the entries in this section.

The patient will also be provided with a Patient Log (P/L) to record medications taken following discharge and to comment on their general status. This log will be collected on VISIT 3.

4.2.4 Materials and Methods

Supplies

The study device and control solution will be provided by DEVICE MED-SYSTEMS without any charge. The study device and control solution will be packaged in sealed boxes so that there is one (1) carton for each patient appropriately labeled with the protocol number and patient number from the randomization schedule. Each box will contain one (1) of the following:

1. 2.5% ADHESIABLOC® Gel, four (4) separate vials each containing 250 mL, or
2. RLS, one package containing at least 1000 mL.

Two (2) part labels, consisting of the affixed part and the tear-off part will be provided with the study device per each bottle. An affixed part will be permanently attached to the study device. Also, a tear-off part, which contains the concealed identity and lot number and which can be revealed by rubbing off the silver paint in case of an emergency, will be attached to the Label Check Form (LCF). Both parts of the label will have enough spaces for entering the patients' initials. The Manufacturer's label, which is to be attached to the control solution, will be provided along with the study label. Three (3) additional tear-off labels will also be provided, such that four (4) labels including one (1) study label and three (3) tear-off labels can be attached to the LCF for either treatment or control.

Storage

All the boxes containing the study device and the control solution will be stored in a refrigerator kept at 37.4 - 44.6°F.

Dispensing of Solution

Approximately four (4) hours prior to the scheduled surgery, the appropriate box will be removed from the refrigerator and warmed to room temperature. The box may be placed in a 104°F warming oven to facilitate the warming process.

When the patient is confirmed as a suitable study subject, the pre-warmed study device or control solution will be distributed by surgical assistant after the surgeon has completed the primary surgical procedure as discussed below. All 1000 mL of the study device or 1000 mL of control solution are to be delivered into the abdominal cavity. The amount of material to be administered (1000 mL) is based on the normal instillation volume of RLS in practice and is believed to be sufficient enough to allow for the floatation of the adnexal structures. A slight excess (3 to 8 mL), the amount that has been added to each

study device vial, will remain in each of the study device vials. Excess control solution (250 mL) will also remain.

The patient's initials will be recorded on both parts of the label, i.e. the tear-off parts and attached parts. All four (4) tear-off labels are to be attached to the LCF. If the patient is determined not to be eligible for the study at the time of surgery, the sealed box will be returned to storage and quarantined from the remaining study clinical supplies. At that time, a reason for the patient's disqualification will also be recorded in the CRF.

Application of Solution

The study device or control solution will only be administered into the peritoneal cavity by surgical assistant after the surgeon has completed the initial surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs, sponges, and materials.

Since the outer portion of each study device and control solution container is not sterile, its contents will be transferred to the sterile field by using conventional aseptic operating room techniques. Instillation will be achieved using large syringes (60 mL catheter tip) fitted with 5 mm diameter urological catheter irrigation canulas.

Administering the study will involve conducting the following procedures:

1. Approximately 500 mL of solution will be administered either directly into the pelvis or through an irrigation canula while the small bowel is still out of the operative field. Distribution throughout the peritoneal cavity can be facilitated by the surgical assistant's hand or probe.
2. The remaining material, approximately 500 mL will be administered after the small bowel has been returned to its normal position. Distribution of the solution over the serosal surfaces can be facilitated by the surgical assistant's hand or probe.

Additional comments may be made on the CRF. The principal investigator will review and sign on the CRF after examining and verifying all of the entries in this section.

4.2.5 Post-Surgical Week 1 - 4 Evaluations (VISIT 3)

Serum electrolytes, hematology (CBC with differential) and blood chemistries will again be conducted at the VISIT 3.

The investigator will also record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-surgical pain, nausea, infection, and etc, between the patient's discharge and VISIT 3. The patient will again be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. These results will be recorded on the CRF.

New P/L will be provided after collecting the first P/L. Prior to completing this visit, the patient will be interviewed to assess any ongoing or new adverse experience(s).

Additional comments may be made on the CRF. The principal investigator will review and sign on the CRF after carefully examining and verifying all of the entries in this section.

4.2.6 Second-Look Laparoscopy (VISIT 4)

The patients will undergo a second-look laparoscopy six (6) weeks to twenty (20) weeks after the initial surgery (minimum of six (6) weeks, maximum not to exceed twenty-four (24) weeks).

Serum electrolytes, hematology (CBC with differential), blood chemistries, and urinalysis (including a urine pregnancy test) will again be conducted prior to the second-look laparoscopy. These data will be recorded on the CRF.

The second P/L will be collected, and the patient will again be interviewed regarding any ongoing or new adverse experience(s). These data will be recorded on the CRF.

The VISIT 4 surgical procedure will be videotaped. The investigator will perform an examination of the peritoneal cavity, unusual lesions or the presence of ascites, and assessment of the presence, severity and extent of adhesions at the same 24 anatomical sites during the surgical procedure. Specific adhesion sites will again be sketched and recorded on the CRF. The presence of endometrial tissue at this VISIT 4 procedure will also be noted for the same 24 anatomical sites and recorded on the CRF. The stage of endometriosis utilizing the mAFS scoring system is also to be noted on the CRF. Also, an optional worksheet will be provided as an aide for recording the adhesion assessment in the operating room.

The patient status will be examined upon study completion or discontinuation and recorded on the CRF. If the potential evaluable patient fails to complete the entire study, ex., intraoperative exclusion criteria applies during initial surgical procedure or does not return for the VISIT 4 procedure, she is considered a screen failure or an early termination respectively, and the reason for the discontinuation will be indicated.

Additional comments may be made on the CRF if needed. The principal investigator will review and sign the CRF after carefully examining and verifying all of the entries in this section.

4.2.7 Concomitant Medications and Adverse Events

The concomitant medications and adverse events will be grouped together in the separate section of the binder since this information is to be gathered throughout all phases of the study.

All baseline and concomitant medications (with the exception of IV hydrating solutions, anesthetics, and muscle relaxants administered during the surgical procedure) will be recorded on CRF, along with a copy of the anesthesiologists report.

The concomitant and baseline medications, including prescription and non-prescription medications will be derived from interviewing the patient or from the following source documents:

1. Patient history (office chart)
2. Patient medication records
3. Pre-operative anesthesia notes and anesthesia records
4. Post-anesthesia care records

All of the above source documents will be made available at the time of monitoring but will not be removed from the study site.

Other medications will also be reviewed by the investigator to determine whether it is considered necessary for the patient's welfare and whether it will not either directly or indirectly modify the actions and assessment of the study solution.

The patient will also be provided with a P/L to record medications taken following the surgery. The patient will be instructed in the use of the P/L and the need to bring the P/L to VISIT 3 and 4. At these visits, the investigators will review the P/L for completeness and accuracy. If the patient fails to return the P/L, this fact will be noted in the comments section on the CRF.

Any adverse events and/or intercurrent illnesses occurring during the study (including the nature, severity and the relation of the incident to the study) solution will also be recorded on the CRF.

5 Statistical Considerations

5.1 Study Populations

The safety populations will consist of all patients who receive 2.5% ADHESIABLOC® Gel or RLS during initial surgical procedure. A subset of the efficacy population will exclude patients who fail to conduct the VISIT 4 procedure. Thus, the evaluable efficacy population will consist of all patients who receive 2.5% ADHESIABLOC® Gel or RLS during initial surgical procedure and who participate in VISIT 4 procedure.

Patients who are randomized but do not receive treatment, i.e. intraoperative exclusion criteria applies during the initial surgical procedure will be described but will not be otherwise analyzed.

5.2 Sample Size

As this is a pilot study, no formal sample size calculation is undertaken. Based on a pilot study evaluating the safety and efficacy of anti-adhesion device in other indication (Baxter Healthcare Corporation, 2000), 46 patients (23 per treatment group) were selected as an achievable number to complete the study. The 40 evaluable patients (20 per group, approximately 50 total enrollments) appear to provide sufficient sample size to reject the null hypothesis if the observed trends are maintained.

The study enrollment number is based on a worse case 30% screen failure rate and 20% loss to follow-up rate. 70 patients will be requested for participation in the study, with 50 expected to receive treatment, and 40 to participate in VISIT 4 procedure. All patients assigned study numbers and receiving treatment will be carefully followed and all screen failure and loss to follow-up patients documented. All efforts will be made to keep these to a minimum.

Any patient who fails to return for the VISIT 3 and/or the VISIT 4 will be contacted and interviewed if possible as to her reason for not returning and her medical status ascertained relative to the effects of the study device. All attempts to contact the patient will be documented on the CRF.

A patient may be discontinued from the study at any time in the event of a serious or intolerable adverse event, the need for an excluded medication, an intercurrent illness, a protocol violation or at the patient's request.

5.3 Safety Considerations

Safety considerations will include patient self-reporting of adverse events categorized using standard COSTART terms. Laboratory values will be recorded as a mean deviation from the baseline and as transition tables showing the proportions of patients above, below and within the normal range (20%) both before and after treatment.

5.4 Efficacy Variables

The primary efficacy variable will be a total adhesion score using the modified American Fertility Society (mAFS) scoring system applied to 24 anatomical sites. Grading the extent of adhesions and the adhesion score derived from severity and extent will be discussed in Appendix III.

Scores from all potential adhesion sites will be averaged (divided into 24) to yield a total adhesion score which will range from 0 to 16. Adhesions will be categorized as either *de novo* or *reformed* depending on their characteristics. Sites with *de novo* adhesions will also be characterized as surgical versus non-surgical.

A secondary efficacy variable, i.e. the proportion of sites with adhesions will also be analyzed. This will be a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. Adhesions will be characterized as *de novo* versus reformed, surgical versus non-surgical as above.

In addition, adhesion sites will be categorized by the presence or absence of endometriosis, use of sutures and the method of adhesiolysis (sharp dissection, cautery, and laser).

Each anatomical site will also be analyzed regarding the severity and extent of all categories of adhesions. Appendix III discusses on Severity and Extent scores.

5.5 Statistical Analysis

Adhesion scores from the records of VISIT 4 procedures will be analyzed using treatment groups (2.5% ADHESIABLOC® Gel versus RLS) as a factor and adhesion scores as a variance. Interactions between baseline adhesion scores and treatment groups will also be examined to test Homogeneity.

Age, race, height, weight, blood pressure, previous and concomitant medications categorized by AHFS codes, presence of endometriosis, surgical-procedures categorized by CPT codes, estimated blood loss, operative time and baseline adhesion scores will be analyzed.

If the two groups differ on any important demographic or surgical variables mentioned above or if these variables appear to strongly predict VISIT 4 adhesion scores by using multiple linear regression with treatment group forced into the model as a dummy variable, these variables may be added to the model as covariates. Interactions between covariates and treatment group will be examined to test the Homogeneity of slopes. Covariates may be transformed in order to yield homogeneous slopes.

The mean proportion of sites with adhesions observed at VISIT 4 will be analyzed in the same fashion as the mean VISIT 4 adhesion scores. Other continuous variables will be analyzed using factorial variance analysis.

Categorical variables will be analyzed by using the Cochran-Mantel-Haenszel test with individual sites as strata. Proportions with small expected event rates such as adverse events will be analyzed using Fisher's exact test. Laboratory value transition tables will be compared by using 2x9 Fisher's exact test. Two-sided p- values will be recorded and p-values less than 0.05 will be considered indicating statistical significance.

6 Other Considerations

6.1 Reporting and Recording of Data

All information required by the protocol will be provided or an explanation given for omissions. All CRFs will be made available as soon as they are completed in order that the monitor may verify the validity and completeness of the forms.

All data and information on these CRFs will be neatly recorded in type or legibly printed in black ink for ease of duplication, interpretation and analysis. If a correction is needed on CRF, the correction will be crossed out neatly with a single line and the new entry initialed and dated by the staff making the correction.

6.2 Records Retention

Federal law requires that a copy of all records (e.g., informed consent documents, laboratory data slips, source documents, safety reports, study device dispensing record, etc.) which support the CRF for this study, be retained in the files of the responsible investigator for a minimum of two years following notification by Device Med-Systems that all studies (not merely the investigator's portion) are discontinued or that the Premarket Approval application is approved by Food and Drug Administration.

If the principal investigator retires, are relocated, or for other reasons withdraws from the responsibility of keeping the study records, custody will be transferred to a person who will succeed the position.

6.3 Adverse Events

All adverse events during the study including the nature, severity and the relation of the incident to the study solution will be recorded on the relevant section on the CRF. A serious adverse event includes one that is life-threatening, results in death, results in or prolongs hospitalization, results in severe or permanent disability, or involves cancer, a congenital anomaly, or an overdose. Device Med-Systems designated contact is:

Jonathan Q. Kruger, MD
Phone: 410-916-3795

There are no anticipated adverse events. The theoretical risks that associated with the use of the study solution are ascites, allergic reactions, sepsis, and wound dehiscence, although these were not observed in preclinical animal testing.

6.4 On-site Audits

The United States Food and Drug Administration may request on-site, including access to all study records, including source documents, for inspection and copying.

6.5 Patient Confidentiality

The investigators may keep key patient information on the CRF, which will be used for the purpose of long-term follow-up, if needed. This form will be treated confidential and will be filed with restricted access. Otherwise, all reports and communications relating to the study will identify patients by assigned patient numbers only.

6.6 Modification of Protocol

This protocol shall not be modified without confirmation of Device Med-Systems. If it is to be modified, the party requesting the modification shall submit written request to Device Med-Systems. Device Med-Systems will then notify Food and Drug Administration of the modification.

6.7 Discontinuation of the Study

This study will be terminated in case of certain administrative condition including, but not limited to, a decision to discontinue further clinical investigation with the device, improper conduct of the study by the investigator(s) or an inability to obtain the number of patients required by the protocol.

APPENDIX I**- Anatomical Sites Evaluated -**

Anterior peritoneum	caudal, right cephalad, left cephalad, incision
Uterus	anterior, posterior
Omentum	
Bowel	small, large right, large left, rectosigmoid large
Cul-de-sac	
Pelvic sidewall	Right, left
Right ovary	lateral, medial, fossa
Left ovary	lateral, medial, fossa
Fallopian tube	right, left
Ampulla	right, left

- Classifications regarding severity and extent of the adhesion(s)² -

Severity	Description
Mild	filmy, avascular adhesion
Severe	dense, organized, cohesive, vascular adhesion
Extent	Description
Localized	less than 1/3 of the site covered
Moderate	1/3 to 2/3 of the site covered
Extensive	more than 2/3 of the site covered

² The extent of adhesions will not be determined for the small bowel, omentum, and large bowel right and left, since their size precludes adequate visualization or evaluation.

APPENDIX II

- Case Report Forms recorded for the evaluations -

Evaluations/Procedures	Schedule of Evaluations				
	VISIT 1	VISIT 2.1	VISIT 2.2	VISIT 3	VISIT 4 ³
Informed Consent	X				
Inclusion/Exclusion	X	X			
Background Information (Demog., Med & Surg. History)	X				
Physical Exam (& Vital Signs)	X		X ⁴	X ⁴	
Concomitant Medications	X	X	X ³	X ^{3,4}	X ⁴
Blood Chemistries	X		X	X	X
Hematology	X		X	X	X
Pregnancy Test / Urinalysis	X				X
Confidential Patient Follow-Up	X				
Device Label Check		X			
Adhesion Assessment		X			X
Suture Use, Surg. Intervention		X			
Endometriosis Evaluation		X			X
Abdominal Drawings		X			X
Adverse Events		X	X	X	X
Patient Status				X	X
Principal Investigator Signature & Comment	X	X	X	X	X

³ Concomitant Medications, Blood Chemistries, Hematology, and Pregnancy Test / Urinalysis are to be completed prior to VISIT 4.

⁴ A limited physical examination prior to discharge and at VISIT 3 is for the purpose of performing an abdominal auscultation and percussion for assessment of the presence of ascites

⁵ Dispense P/L.

⁶ Collect P/L.

APPENDIX III**- Extent of adhesion⁷ -**

Localized	Moderate	Extensive
<1/3 of site covered	1/3-2/3 of site covered	>2/3 of site covered

- Severity Score -

None	0
Mild	1
Severe	4

- Extent Score -

None	0
Localized	1
Moderate	2
Extensive	4

- Adhesion scores using AFS scoring system -

Severity and Extent of adhesion	Score
No Adhesion	0
Severity: Mild Extent: Localized	1

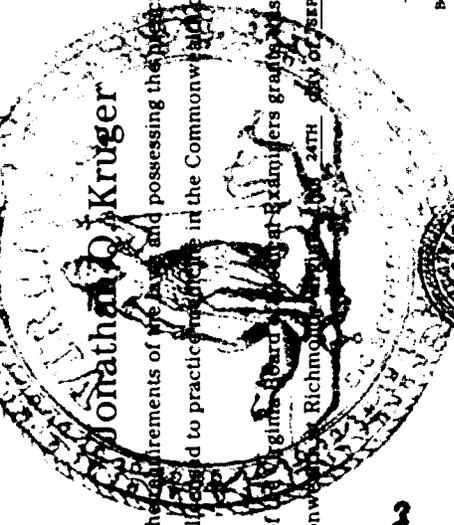
⁷ The extent of adhesions will not be scored for the small bowel, omentum and left and right large bowel since their size precludes adequate visualization. These sites will be assigned a classification of Moderate in order to determine the total adhesion score.

Investigational Device Clinical Protocol No. P-D015 Ver. 1.4, Device Med-Systems

Severity: Mild Extent: Moderate	2
Severity: Mild Extent: Extensive	4
Severity: Severe Extent: Localized	4
Severity: Severe Extent: Moderate	8
Severity: Severe Extent: Extensive	16

Commonwealth of Virginia

BOARD OF MEDICAL EXAMINERS



Having fulfilled all the requirements of the law and possessing the prescribed qualifications,
 Is hereby licensed to practice medicine in the Commonwealth of Virginia

In witness whereof the Virginia Board of Medical Examiners grants this license under the
 seal of the Commonwealth of Virginia this 24TH day of SEPTEMBER 1990

[Signature]
 CLYDE SECRETARY
 VIRGINIA BOARD OF MEDICINE

[Signature]
 PRESIDENT
 BOARD OF MEDICAL EXAMINERS
[Signature]
 DEPUTY COMMISSIONER,
 OFFICE OF PROFESSIONS

LIC. 0101261366



**Site Application Checklist
(For Full Board Review)**

PI Last Name: Kruger Study #: Device Med-Systems P-D015

CA MA PR Translations Spanish Other Ads Single Site

Section 1.0- For CIRB Staff: Completed by: JG (initials) Date: 10.27.08

Must have: SSF CV Current License

May have: Attached consent SOP Addl Sites # FDA info 1572
 IRB Waiver Addl study materials Attached ICF change

1. Is Site application complete, including required credentials? Yes No

If no, what is missing or incomplete (Include Date site contacted)

- a. _____
- b. _____
- c. _____

2. Does research study involve vulnerable population/subjects? Yes No

Section 2.0- For Board Member Use

1. Are PI credentials, research experience and support staff adequate to support the study? Yes No N/A

2. Are community attitudes sufficiently documented? Yes No N/A

3. If question #2 above is checked yes for vulnerable subjects, does the site document additional measures employed to protect vulnerable subjects? Yes No N/A

4. Is ICF process adequate? Yes No N/A

***Note, conditions of approval or reasons for disapproval will be discussed during the board meeting and documented in the board meeting minutes.

Board member Initials: [Signature] Date: 10/30/08

Study Mgmt Screen updated: Upon receipt After approval

COAST IRB, LLC
BOARD MEETING Minutes

Board Meeting Date: October 30, 2008
Board Meeting Start Time: 6:00 P.M. MDT
Board Meeting Location: Coast IRB, LLC
5475 Mark Dabling Blvd.
Suite 351
Colorado Springs, CO 80918
- or -
Conference Call: [REDACTED]
Pass Code: [REDACTED]

I) [REDACTED] By Melissa Cortes, M.Ed., Chairperson Meeting Start Time 6:07 PM MDT

II) [REDACTED]

Board Members:

Melissa Cortes, M. Ed. Chairperson Joel Cherlow, M.D., Ph.D. Rochelle Salmore, M.S.N., R.N.
Koren Barrett, N.D. Vice Chair Adam Dodd, M.D. Lawrence Selman, B.B.A.
Pamela Geddis, M.D.

Non-Board Members:

Christy Gorey, Senior IRB Administrator Kathy Self, Regulatory Affairs Specialist Susan Wampler, IRB Administrator
Kim Lenda, Compliance Associate, Secretary

[REDACTED] was not in attendance from 6:34 PM MST to 6:35 PM MST. [REDACTED] was not in attendance for Section(s):
VI.C.1. Items for Board Review: Changes to Research: Sponsor Submitted Changes – Protocol Amendments/Updated
Investigators' (Device) Brochures.

a) [REDACTED]

III) [REDACTED]

A. **Conflict of Interest:** Chairperson asked if any board members had to abstain from any agenda items.

[REDACTED]

B) [REDACTED]

1) [REDACTED] None

2)

(a) **Device Med-Systems- P-D015** -Pilot Study of Safety and Efficacy of 2.5% Adhesiobloc® Gel to Reduce Adhesions Following Peritoneal Cavity Surgery

- (i) **For Review: Protocol, Version 1.4** Adam Dodd, M.D.
 • Decision/Vote: Approve # Voting: 7 # For: 7 # Against: 0
 # [Abstain/Recuse]: 0 Names(s): [Enter member's name]
- (ii) Consent to Participate in a Research Study, Version 1.0 Adam Dodd, M.D.
 Melissa Cortes, M.Ed.
 • Decision/Vote: Conditionally approve # Voting: 7 # For: 7 # Against: 0
 # [Abstain/Recuse]: 0 Names(s): [Enter member's name]
- (iii) **Investigator: Jonathan Q. Kruger, M.D.** Melissa Cortes, M.Ed.
 • Community Attitudes: Community Attitudes were sufficiently described
 • Decision/Vote: Approve # Voting: 7 # For: 7 # Against: 0
 # [Abstain/Recuse]: 0 Names(s): [Enter member's name]

- **Discussion:** New study, device, using a gel post-surgery. This is a single site study, 70 female adults who are already undergoing laparotomy due to infertility, pain and or/irregular vaginal bleeding with preservation of fertility. Already have planned 2nd look laparoscopy, within 6 months after the surgery. This is a double blind study in the sense that after the surgery is completed either the gel or saline is introduced by a third party. Doctor performing the surgery does not know and the subject does not know whether the patient has received the gel or the saline. This is the first study using this gel in humans, though similar devices/substances have been used in the same way, with the goal to see if it prevents adhesion formation after surgical procedures in which adhesion is a risk. This study is targeting a population where the majority of the subjects will be having surgery for reasons of preserving their fertility, therefore adhesions could negatively impact the outcome. The subjects will not be receiving reimbursement. They may participate or not, and their decision does not affect treatment. The continuing review interval recommendation is 6 months (semi-annual) even though the gel is probably very safe; this is a pilot study & first-time use in humans. Recommendation is for conditional approval of the ICF, as terms need defining. Sponsor was unable to provide the definitions pre-meeting. The protocol looks fine. The Board Chair questions whether, given this population, this specific set of patients undergoing certain procedures regarding fertility, whether they would be familiar with the vocabulary used in the consent anyway? Primary says most likely yes, and many of the words in the consent form will be associated with other procedures already covered by different consent forms from their doctor. The Safety Reviewer notes that neither the protocol nor the consent form defines or offers guidelines when discussing "significant accumulation of abdominal fluid or ascites" - Should this be spelled out and "significant" in particular defined? The Primary has no problem asking sponsor to be more specific but this parameter is not what is being looked for the purposes of the study, so it is not that imperative. The observation has to do with fluid in the abdomen, and is not critical to study procedures. Also, the Safety Reviewer has a concern or question about leaving extra fluid in the abdomen - is this standard procedure? The Primary says this is not a bad thing, it provides a buffer post-surgery to prevent adhesion. Gel substance is more sticky, stays in place during healing process and scar formation and ovary or tube heals. The gel might prevent adhesion more effectively since it does not move around as freely as a fluid. Recommendation is for approval of the protocol and the site, which the Board Chair had no issues with, and conditional approval of the ICF. The ICF can come back expedited to Chair and Primary once definitions are provided by the Sponsor.
- Vulnerable Population: No
- Significant Risk Assessment: Not applicable - 510(k) device
- Set Continuing Review: 6 months (semi-annual)
- Continuing Review Rationale: Pilot study, new device in humans
- Action Item (s): None
- Submitted by: Denise Strasser

Version #2

V3F 06.13.08

IV) [REDACTED]

This agenda has been respectfully submitted by Coast IRB, LLC Compliance.

Susan Wampler, IRB Administrator
On behalf of Coast IRB, LLC Compliance

Adjourned by: Melissa Cortes, M.Ed. Chairperson

Time: 7:01 PM MDT

Submitted by: Kim Lenda, Compliance Associate, Secretary

Approved by: _____
Melissa Cortes, M.Ed, Chairperson

_____ Date

Next Meeting Date: Tuesday November 04, 2008

Pam Peinado

From: Denise Strasser
Sent: Thursday, October 30, 2008 1:46 PM
To: Christy Gorey; StartupGroup
Cc: Susan Wampler
Subject: RE: DR. DODD AND MS. CORTES REDLINE/SPONSOR QUESTIONS === FW: DMS ICF(a) Device Med-Systems- P-D015 10.30.08

Hello back!!!

ICF - I have sent the request for change of the icf to the sponsor with explanation. I gave him the deadline of 4:00 pm to return the icf to me and if not possible by 4:00 then we would have to "conditionally approve" the form and send back for review at a later date.

The 510k information - The FDA has registered this device as a 510k (registration # K073692). Under a 510k, the device does not have to be exactly the same as another product on the market but it does have to have similarities to something on the market. I am unable to quote what qualifies as a 510k but this product does have a registration # under a 510k. I think this information should be sufficient but if it is not, let me know and I will get other specifics from the sponsor.

Thanks for facilitating! I will forward the icf if I get it back today!!!

Denise Strasser
New Studies Service Lead

Coast IRB, LLC | www.coastirb.com
5475 Mark Dabing Blvd, Suite 351
Colorado Springs, CO 80918
P [REDACTED]
F [REDACTED]

Please visit www.coastirb.com/service and let us know how we are doing!

From: Christy Gorey
Sent: Thursday, October 30, 2008 10:14 AM
To: StartupGroup
Cc: Christy Gorey; Susan Wampler
Subject: DR. DODD AND MS. CORTES REDLINE/SPONSOR QUESTIONS === FW: DMS ICF(a) Device Med-Systems- P-D015 10.30.08
Importance: High

Hello ~

Please see Dr. Dodd and Ms. Cortes emails below regarding the Consent (attached) and 510K rating for the Device Med-Systems P-D015. Please provide me with the information and I will submit to both Board Members.

With thanks,

Christy Gorey
Senior IRB Administrator

2/24/2009

Coast IRB has moved! Please note our new address:

Coast IRB, LLC | www.coastirb.com
5475 Mark Dabing Blvd, Suite 351
Colorado Springs, CO 80918

P [REDACTED]

F [REDACTED]

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From: Adam and Laura Dodd [REDACTED]
Sent: Thursday, October 30, 2008 9:01 AM
To: M. Cortes; Christy Gorey
Subject: Re: DMS ICF

M ~

I would favor sending back to sponsor for definitions. This is a good study, so I'm planning to recommend conditional with expedited of ICF back to you and I. If the sponsor was willing to do that before the meeting, I'd be happy to look at it and remove the conditional.

I would also like to know on what basis this is a 510K?

My understanding of 510Ks and risk assessment is that it's premarketing and that there has to be a clinically identical product already on the market which has a safe risk assessment by the FDA, and I'm not aware of any gets already approved for these indications. Just checking for my info and education. It won't affect my recommendation.

Also, the email address [REDACTED] pops into my phone. I'm on the run today, but if you need me to look at something feel free to use that one, too.

AD

----- Original Message -----

From: M. Cortes
To: Christy Gorey ; Adam Dodd ; Adam Dodd
Sent: Wednesday, October 29, 2008 7:08 PM
Subject: DMS ICF

Hello,

For whatever reason, I was unable to save my ICF changes for the DMS study on the board website. This ICF, IMO, is atrocious! It is riddled with medical speak that will either have to be re-written in lay terminology, or at the very least, have parenthetical definitions inserted throughout. At many points, it looks like a cut and paste from the protocol. It is just too sophisticated and difficult to understand. Adam, I don't know if you are up to the challenge of rewriting this ICF (transforming medical language to lay language) or if we should send it back to the sponsor for revisions...

Melissa

2/24/2009

*trial***Consent to Participate in a Research Study**

Study Title: Pilot Study of Safety and Efficacy of 2.5%
ADHESLABLOC® Gel to Reduce Adhesions Following
Peritoneal Cavity Surgery

Sponsor: Device Med-Systems

Protocol Number: P-D015

Principal Investigators: Jonathan Q. Kruger, M.D.

Address: Device Med-Systems
5746 Union Mill Road
Clifton, Virginia 20124

Telephone: [REDACTED]

After Hours: N/A

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason.

Research studies are designed to obtain new knowledge that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or Device Med-Systems. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researcher ("investigator") named above, or the research staff members who may assist him, any questions you have about this study at any time.

What is the purpose of this study?

You have been asked to be in the study because you are a woman over the age of 18 undergoing a certain type of abdominal surgery. It is possible that harmful adhesions may form in your abdomen after this surgery. Adhesions are similar to scar tissue and might prevent you from having children in the future.

Approved by Coast IRB, LLC
November 6, 2008
Page 1 of 5

This study is testing a product that might reduce or block these adhesions from forming. The product is called ADHESIABLOC® Gel. Although there are other methods to reduce or block adhesions, this study wants to find out whether ADHESIABLOC® Gel is as safe and effective as the other methods.

Are there any reasons you should not be in this study?

You should not be in this study if you:

1. are pregnant or lactating
2. are undergoing tubal sterilization ("getting your tubes tied"), reversal of sterilization, or certain other similar procedures (e.g. "tubal implantation") during the surgical procedure
3. are receiving cancer therapy including drugs and radiation within 3 weeks prior to your surgery
4. are suffering from coagulation disorders (related to either your blood or your lymph fluids), or are taking anticoagulants (medicines intended to prevent clotting)
5. have a history of hemochromatosis (a disease characterized by excessive absorption of iron in your diet)
6. have liver (hepatic) or kidney (renal) disorders
7. are diabetic and are taking oral or injected hypoglycemic medications
8. are suffering from any immune system deficiencies or disorders
9. are unsuitable for processing large fluid loads (e.g. patients with congestive heart failure)
10. have any absorbable instruments to stop bleeding (a hemostat) left in your abdomen
11. are receiving any other adhesion prevention agents, particularly those containing corticosteroids, NSAID's, or HYSKON® (Dextran)
12. will require medication or other liquids to be injected through your cervix into your uterus or fallopian tubes (post-surgical hydrotubation)
13. have an active pelvic or abdominal infection
14. will undergo peritoneal grafting (in which healthy tissue is taken from one part of your body to replace injured tissue in another part of your body) as part of your operative procedure
15. require any surgical procedure at the time of the initial surgical procedure (laparotomy) that involves opening the gastrointestinal or urinary tract
16. are found to have adhesions in 12 or more of the 24 anatomical sites examined as part of your initial operative procedure
17. will have one or more of the 24 anatomical sites removed during your initial operative procedure

How many people will take part in this study?

If you decide to be in this study, you will be one of approximately 50 people in this research study.

How long will your part in this study last?

The total study will be up to 20 weeks, from the first surgery to a second procedure that will look at your abdomen to determine whether any adhesions have formed (maximum not to exceed 24 weeks).

What will happen if you take part in the study?

This will be a double-blind study, which means that neither you nor the researcher will know if you are receiving ADHESIABLOC® Gel or an existing method of reducing or blocking adhesions. In case of an emergency, however, your course of treatment can be found through Device Med-System's records.

The following procedures will be performed on all subjects:

1. Initial Operative Procedures

Prior to your discharge from the hospital after your initial surgical procedure or within 4 days of the surgery, a series of tests (serum electrolytes, hematology and blood chemistries) will be performed. The investigator will record any adverse experiences that you note and/or those observed by the staff. By adverse experiences, we mean those that could include post-operative pain, nausea, infection, etc. The examination will also determine if there is too much fluid in your abdomen. In addition, you will be provided with a diary to document medications taken following discharge and to comment on your general status and health.

2. Check-Up Evaluations

Medical tests (serum electrolytes, hematology and blood chemistries) will again be performed at a check-up visit within 4 weeks after the initial procedure. The investigator will record any adverse experiences noted by you and/or observed by the staff. You will again be examined to determine if there is too much fluid in your abdomen. Your patient diary will be retrieved and a new one will be provided to you. Before you finish this visit, you will be interviewed regarding any ongoing or new adverse experiences.

3. Second-Look Operative Procedures

You will undergo a second-look procedure about 6 to 20 weeks following the first procedure (not to exceed 24 weeks). Prior to the surgery, some medical tests (serum electrolytes, hematology, blood chemistries, and urinalysis--including a urine pregnancy test) will again be performed. Your patient diary will be retrieved, and you will be interviewed regarding any ongoing or new adverse experiences. The second procedure will be videotaped. During the procedure, the investigator will perform an examination of your abdomen to determine whether you have any adhesions, excessive abdominal fluid, or other problems.

What are the possible benefits from being in this study?

This study will benefit society by allowing it to gain new knowledge on how to reduce or prevent adhesions. In addition, your participation in this study may reduce your risk of getting adhesions after your surgery.

What are the possible risks or discomforts involved with being in this study?

There are no known side effects or discomforts associated with ADHESIABLOC® Gel, but there may be uncommon or previously unknown risks. You should report any problems to the investigator or staff.

We do not know the effect of ADHESIABLOC® Gel on babies before they are born, or on nursing children. If you are planning to get pregnant, you should not be in the study. Pregnancy

Approved by Coast IRB, LLC

November 6, 2008

Page 3 of 5

tests will be done on all women who might be able to get pregnant at the start of the study. These tests will be paid for by Device Med-Systems. If you become pregnant during the study, you should notify the investigator immediately.

If you choose not to be in the study, what other treatment options do you have?

You do not have to be in this research study in order to receive treatment. For other available treatments that may benefit you, please consult the investigator and staff.

What if we learn about new findings or information during the study?

During the course of this study, if we find or learn anything new that might make you want to stop participating, we will share this information with you.

How will your privacy be protected?

We will not identify you by name in any report or publication about this study. Although your privacy is essential to us and we try to keep our study records private, it is possible that a federal or state law may require us to disclose personal information about the patients in our study. Although this is not likely, Device Med-Systems will try to protect the privacy of your personal information in this situation. It is also possible that research sponsors, government agencies, the FDA, and Device Med-Systems staff will need to see your personal information for safety reasons.

A copy of this consent form will go into your medical record. This will allow the doctors caring for you to know that you are participating in this study. This information will help them to take care of you in case you have any health problems.

What will happen if you are injured by this research?

All research involves a chance that something adverse might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or get an injury from being in this study. If such problems occur, the investigator and staff will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. Device Med-Systems has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. Upon your withdrawal you will no longer be enrolled in the trial and no further study procedures will be performed nor additional data will be collected. Any data collected prior to your withdrawal will continue to be used in connection with the study. If you choose to withdraw from this study you must notify the study doctor at the phone numbers listed on page 1 of this consent form for instructions on withdrawing from the study.

Can participation be terminated without the subject's consent?

The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Approved by Coast IRB, LLC
November 6, 2008
Page 4 of 5

Will you receive anything for being in this study?

You will not be compensated for taking part in this study.

Will it cost you anything to be in this study?

Although you will be billed for your routine medical care, it will not cost you anything extra to be in this study. The tests, visits or procedures that you will receive as part of this study will be the same as the care that you would normally have received for your surgery even if you had not participated in the study. You will be required to provide your own transportation to and from the study test site.

Who is sponsoring this study?

This research is funded and conducted by Device Med-Systems. The investigator and staff do not, however, have a direct financial interest in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or if a research-related injury occurs, you should contact the investigator listed on the first page of this form.

What if you have questions about your rights as a research subject?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact Coast Independent Review Board at (719) 325-8400, Monday - Friday, 8:00 a.m. - 5:00 p.m. Mountain Time. Collect calls will be accepted.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

Signature of Research Subject

Date

Printed Name of Research Subject

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent

Denise Strasser

From: Lisa Bean
Sent: Tuesday, January 13, 2009 2:30 PM
To: information@[REDACTED]
Cc: Denise Strasser
Subject: FW: Thank you

Good afternoon Paul,

I hope your day is going well. I have contacted a few of our customers and they would be happy to talk with you. The first young lady I spoke with is Luz Zimmermann from Novartis her telephone number is [REDACTED]. The second young lady I spoke with is Margarita Virgil from PRA International (Abbott) her telephone number is [REDACTED]. I would be more than happy to provide you with more contacts if you wish. Please let me know if there is anything else that I may do for you. Look forward to talking with you soon.

Have a fantastic afternoon.

Warm regards,

Lisa Bean
Customer Relationship Specialist

Coast IRB, LLC | www.coastirb.com
5475 Mark Dabbling Blvd. Suite 351
Colorado Springs, CO 80918
[REDACTED]
[REDACTED]

Please visit www.coastirb/service and let us know how we are doing!

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Hello Paul,

Thank you for your inquiry. I will do some investigating on my end and see what I can put together for you in the means of references/referrals. If in the meantime you should need any additional information please feel free to contact me. I will be in touch soon.

Have a fantastic evening.

Warm regards,

Lisa Bean
Customer Relationship Specialist

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5475 Mark Dabbling Blvd. Suite 351
Colorado Springs, CO 80918
P [REDACTED]
v [REDACTED]

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-----Original Message-----

From: information [REDACTED]
Sent: Monday, January 12, 2009 9:50 AM
To: Lisa Bean
Cc: Denise Strasser
Subject: Re: Thank you

Lisa,

I hope you've been having a great New Year. Thank you for the information on Coast's customer service. It was very helpful! I was also looking at your web site and saw on your "Clients" link that you've done some work for some pretty big companies (AstraZeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, etc). Do you have any referrals/references at those companies, people we could speak with regarding their experiences with Coast? That would be a big help.

Thanks again for all of your help,

Paul

Paul Jennings
Device Med Systems
5746 Union Mill Rd
Clifton, Virginia 20124

> Good afternoon Paul,
>
>
> I hope that your day is going well. I want to thank you for choosing
> Coast IRB for the review of your study.
>
>
> Please find attached a couple of brief pieces that describe Coast IRB.
>
>
> Coast IRB was recently named by INC Magazine as one of the fastest
> growing companies in America. This prestigious accolade is due to our
> desire to stick with the 3 main philosophies that our founder Darren
> McDaniel used to start Coast IRB; speed, quality and flexibility. Our
> board meets twice per week and documents are shipped the day following
> the board meeting. Coast IRB is big enough to have individual account
> teams that are assigned to your project but small enough to allow you
> flexibility in how documents are processed, shipped, etc. All
> documents are checked for quality up to 3 times prior to release to our customers.
>
>
> If you want an IRB with experience, Coast IRB has it. Coast IRB has
> worked on over 1000 multi-center trials ranging in size from 5 sites
> to over 400 sites in all phases of development. Coast IRB has
> approved over 15,000 Primary Investigators and we are currently
> servicing over 400 ongoing clinical trials.
>

>
>
> A couple of months ago we sent an email to several customers asking
> for them to fill out a survey on the quality of our service. We
> expected to receive a few responses per week from the busy Clinical
> Research Associates that we work with daily. To our delight, we have
> received 81 positive responses and 1 negative response which was
> corrected the same day. Below are just a few of the comments that we
> have received. Would you say these statements about your current IRB?
>
>
> "Thank you very much you guys are the quickest IRB I have ever worked
> with and I have done this 7 years! Thanks"
>
>
> There has been such great service to date."
>
>
> "EXCELLENT!!!!!!!!!"
>
>
> "I have been satisfied with Coast's service throughout study start-up
> and continuing review."
>
>
> I am always appreciative of the helpfulness and friendliness of the
> staff at Coast.
>
>
> I want to thank you all for your fabulous work on this project. I
> understand that we have been asking a lot from you lately and you have
> handled it with grace and poise every time. I know from my own
> experience working in a Central IRB, that all of the abovementioned
> tasks take time and a lot of effort from the staff. Thank you again
> for all of your help with these matters. Your efforts are greatly
> appreciated!
>
>
> I hope the information provided has been inspiring. We look forward to
> continuing business with you.
>
>
> Have a wonderful Holiday Season! :-)
>
>
> Warm regards,
>
>
> Lisa Bean
> Customer Relationship Specialist
>
>
> Coast IRB, LLC | www.coastirb.com <<http://www.coastirb.com/>>
> 5475 Mark Dabbling Blvd. Suite 351

>
> Colorado Springs, CO 80918
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> P [REDACTED]
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> F [REDACTED]
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> notify the author by replying to this e-mail immediately.
>
>
>
>

Peter Arhangelsky

From: Dan Dueber [REDACTED]
Sent: Friday, March 06, 2009 1:23 PM
To: Jonathan Emord
Cc: Peter Arhangelsky; Andrea Ferrenz
Subject: RE: Letters to federal officials and the Va Board for your review

Hi Jonathan --- this seems sensible to me. In our existing position, I feel it is wise to stay on offense. So I agree with doing a press release.

Tx Dan

Dan Dueber
 President, CEO and Manager of LLC

Coast IRB, LLC | www.coastirb.com
 5475 Mark Dabing Blvd, Suite 351
 Colorado Springs, CO 80918

P [REDACTED]
 C [REDACTED]
 F [REDACTED]

Please visit www.coastirb.com/service and let us know how we are doing!

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From: Jonathan Emord [REDACTED]
Sent: Friday, March 06, 2009 12:44 PM
To: Dan Dueber
Cc: Peter Arhangelsky; Andrea Ferrenz
Subject: RE: Letters to federal officials and the Va Board for your review

Hi Dan--We will verify receipt of all the letters to the federal and state agencies on Monday. We will then issue the email with the letters and the board resolution attached to the staff of Energy and Commerce either late Monday or Tuesday. If we receive no response, I am inclined to have you outmaneuver the committee by having a press release announce the find and action by Coast IRB in a light favorable to you about a week before the hearing date.

The aim would be to get good publicity out there about how effective Coast had been in spotting a fraud and pursuing it, while also explaining how Coast protects human subjects of clinical research. Aware that adverse publicity could be generated and could lump Coast in with bad actors from the hearing testimony, it might be good to steal their thunder in this way. Does this interest you? If so, I will put together a press release and recommend a person to dispatch it professionally.

Jonathan

00042A

From: Dan Dueber [REDACTED]
Sent: Fri 3/6/2009 1:54 PM
To: Andrea Ferrenz
Cc: Jonathan Emord; Peter Arhangelsky; Pam Peinado
Subject: RE: Letters to federal officials and the Va Board for your review

Dustin caught this: the Board voted and approved the termination of this study. It was not suspended. So, please change the first paragraph accordingly.

Thanks! Dan

Dan Dueber
 President, CEO and Manager of LLC

Coast IRB, LLC | www.coastirb.com
 5475 Mark Dabling Blvd, Suite 351
 Colorado Springs, CO 80918

P [REDACTED]
 C [REDACTED]
 F [REDACTED]

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From: Andrea Ferrenz [REDACTED]
Sent: Friday, March 06, 2009 11:06 AM
To: Dan Dueber
Cc: Jonathan Emord; Peter Arhangelsky; Pam Peinado
Subject: Letters to federal officials and the Va Board for your review

Dan,

Please find attached the letters to the federal law enforcement officials that would be the most interested in the recited facts. Those letters are identical to one another save for the addressee. The letter to the Virginia Board (Department of Health Professions) is focused on the licensure issue.

Please review these documents and let us know if they are approved to send. If you have any edits or concerns please do not hesitate to contact us. I will be in the office until 2:30. Jonathan is available at [REDACTED]. Please be certain to copy our associate Peter Arhangelsky on this correspondence. He will take care of sending the documents. I have copied him on this email.

Thanks,
 Andrea

Andrea G. Ferrenz
 Emord & Associates, P.C.
 11808 Wolf Run Lane
 Clifton VA 20124
 Ph: [REDACTED]
 Fx: [REDACTED]

00042A

[REDACTED]

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00042A

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PRESS RELEASES

PRESS RELEASES

FOR IMMEDIATE RELEASE: 3/10/2009

CONTACT: Diane Morrow (800-927 1517) or cell [REDACTED]

Clinical Trial Fraud Detected by Independent Review Board, Reported to Federal and State Authorities

Washington, D.C.: On Friday, March 6, 2009, Coast Independent Review Board, an independent review board that has protected human subjects in thousands of clinical trials, discovered that a protocol submitted to it for review of a medical device called Adhesiabloc by a Device Med Systems of Clifton, Virginia, was in fact fraudulent in violation of federal and state law. Upon receipt of proof of the fraud, Coast IRB and its CEO, Danjel Dueber, ordered the immediate termination of the clinical trial, referred evidence to federal and state authorities for investigation and prosecution, and instituted measures to prevent a recurrence.

Coast IRB notified the Criminal Fraud unit of the U.S. Department of Justice, the Federal Bureau of Investigation, the Food and Drug Administration, and the Commonwealth of Virginia Department of Health Professions of the fraud. Coast IRB has urged authorities to investigate and prosecute the perpetrators whose actual identities remain unknown. Several felony fraud violations and potential RICO may have been committed.

"We are informing the media in the hopes of alerting those who might otherwise become study subjects that this appears to be a fraudulent trial," said Coast IRB CEO Daniel Dueber. "We are also doing so because we want other institutional review boards to learn of our experience and avoid review of this trial pending the result of federal and state investigations," he said.

Coast IRB discovered evidence of the fraud in a routine audit of the trial. In particular, Coast IRB discovered that credentials for the principal investigator for the trial were forged and that neither the principal investigator nor the medical director were licensed in the Commonwealth of Virginia. The Department of Health Professions of the Commonwealth of Virginia from whence the forged license was allegedly issued reported no record of ever granting a license to the person involved, no record of the license number listed on the forged credentials, and no issuance of licenses in the history of the Commonwealth in the format presented by the study sponsor. Coast IRB further discovered through an on-site visit that the address for the clinical trial organization where testing was presumably taking place, 5746 Union Mill Road, Clifton, Virginia 20124, was in fact a strip mall (The Colonnade) in Clifton, Virginia. Finally, a 510(k) FDA number given for the medical device did not exist in FDA's records.

Coast IRB has supplied information concerning the fraud to the House Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee, which is now investigating FDA regulation of human clinical trials. "We are shocked and dismayed by these developments," said Coast IRB CEO Daniel Dueber. "We are pleased, however, that we uncovered the apparent

fraud and alerted federal authorities. I hope those responsible are identified, investigated, and, if guilty of federal and state crimes, prosecuted to the full extent of the law," he said. "We are cooperating with the FDA and law enforcement on the federal and state levels to ensure that those responsible account for their wrong-doing."

Coast IRB is one of the largest independently owned IRB's and was founded in 2002. Its mission is to protect the rights and welfare of subjects in clinical trials by providing an ethical and thorough review in a timely and efficient manner. Coast IRB is proud of its history of providing ethical services with high integrity. It is located in Colorado Springs, Colorado.

###

[About Us](#) | [The Coast Difference](#) | [Sponsors](#) | [Site](#) | [Research Participants](#) | [Our IRB Process](#) | [News & Events](#) | [Contact Us](#)
Coast IRB, LLC • 5475 Mark Dabbling Blvd, Suite 351 • Colorado Springs, CO 80918 • 719.325.8400
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Re Fw Re Protocol Submission 2009-11-10.txt
From: information@devicemedsystems.com
Sent: Monday, November 10, 2008 1:46 PM
To: Valerie A Golembiewski
Subject: Re: Fw: Re: Protocol Submission

Valerie,

Thank you for your e-mail. I apologize for the delay in getting back to you. We are withdrawing at this time due to product development.

Thanks again,

Paul

> Argus has not received a reply to the message below.

> Will you be submitting the revisions?

> Thank you.

> Valerie Golembiewski
> Chair
> Argus IRB< Inc.

> ----- Forwarded message -----
> From: Valerie A Golembiewski <argusirb@██████████>
> To: information@devicemedsystems.com
> CC: argusirb@██████████
> Date: Mon, 3 Nov 2008 09:24:01 -0700
> Subject: Re: Protocol Submission
> Message-ID: <20081103.092401.484.0.argusirb@██████████>

> Paul,

> Attached is an explanation of the findings by Argus concerning its review of Adhesiabloc.

> Please have these items reviewed by the appropriate people and respond to Argus with your comments.

> Also advise if you have any questions.

> Argus does not accept credit card payments. Payments should be made via check payable to Argus IRB, Inc., and are payable 30 days after receipt of invoice.

> Thank you.

> Valerie Golembiewski
> Chair
> Argus IRB, Inc.

> On Wed, 29 Oct 2008 16:20:54 -0400 (EDT)
> information@devicemedsystems.com

> writes:
>> Valerie,

>> Good afternoon. We would like to submit our attached protocol for approval. Please refer to the attached files for your review.

>>

Re Fw Re Protocol Submission 2009-11-10.txt
> quote and debt consolidation information. Click Here.
> <http://thirdpartyoffers.juno.com/TGL2141/fc/Ioyw6i3m2Xh91UEYr7HFgU8drv>
> LHT
> v0UdVG6qbcz5Efr20wyfEY4TF/

...

Device Med-Systems

Argus has reviewed your submission for the Pilot Study of Adhesiabloc and has the following comments and questions:

1. The title page of the protocol needs signatures and dates.
2. On page 5 of the protocol, second paragraph, it states that a surgical assistant (third party) will administer the solution. Who is this third party? Is he/she an employee of Device Med or the hospital, or someone else?
3. Argus needs a copy of the CRF.
4. Argus needs a copy of the diagram used to record the incision lines, as well as the optional worksheet.
5. Argus needs a copy of the Patient log as well as the patient diary.
6. A separate consent form is needed for the Visit 4 surgical procedure which will be videotaped. If this is included in the hospital's consent form, please provide a copy of that form.
7. Page 11 of the protocol states that 4 source documents will be made available at the time of monitoring but will not be removed from the study site. Patient consent is needed for that.
8. If the FDA requests an on-site audit, Argus needs to be notified.
9. Where will the surgeries take place? Does this site's consent form cover any of the study procedures?
10. Does the surgeon need to consent? If so, Argus needs a copy of that form.
11. Has the surgeon and/or hospital read the protocol and do they agree?
12. How are the hospitals and surgeons selected? IS there any conflict of interest?
13. Where will the patient referrals come from? Area doctors, etc?
14. It is suggested that a pregnancy test be performed closer to the surgery date since it is possible for a woman to become pregnant in the suggested three week time frame.
15. Who is the manufacturer of Adhesiabloc and where is it made?
16. There is no HIPPA provision in the submitted documents.
17. The consent form should have a space for the patient's initials on each page of the form.
18. The first page of the consent form should list the telephone numbers of Dr. Bradshaw and Dr. Kruger.
19. Convert ml to an amount the average person can understand (e.g. four cups).
20. Clarify all technical language. For example, on page two of the consent form, it is suggested to clarify hematological as hematological (blood) disorders, etc.
21. Is the second surgery considered elective? Who pays for that surgery?
22. Where will the second surgery take place? Will it be performed by the same surgeon?
23. Is this second surgery considered usual practice?
24. Does the risk involved in the second surgery outweigh the benefits?
25. Argus needs Dr. Bradshaw's CV.
26. The consent form does not list alternative treatments as required by the FDA.

27. Page 4 of the consent form states that "the investigator will perform a gross examination". Who is this investigator?
28. Who will perform the taking of the tissues and biopsies?
29. Where will the histology information be recorded?
30. Will the patient be advised of any unusual findings?
31. In the section titled **What are the possible risks or discomforts involved with being in this study**, it should state that the procedure may **not** reduce the risk of post operative peritoneal adhesions, as well as the risks associated with retention of fluid volume.
32. If the patient is not being compensated for being in the study, who pays for the costs associated with the surgeries?
33. In the section titled **What if you have questions...**include the fact that the subject may contact Argus IRB, Inc. at 520-298-7494 also.
34. It is redundant to state the title of the study and the principal investigators on page 6 of the consent form since this is already stated on page 1.

Stith-Coleman, Irene E (HHS/OPHS)

From: Carome, Michael
Sent: Tuesday, June 03, 2003 11:51 AM
To: Kaneshiro, Julie A; Schwetz, Bernard A; Odwazny, Laura; Stith-Coleman, Irene; Higgins, Yvonne; Hicks, Shirley; Borrer, Kristina
Subject: RE: Follow-up on FDA's ANPRM on "IRB shopping"

In my four years doing compliance oversight work, concerns about IRB shopping or noncompliance resulting from IRB shopping were never raised by a complainant or detected by OPRR/OHRP. I agree with Julie that this is rarely a problem. What is far more common is research being done without any IRB reviewing the research.

Mike

-----Original Message-----

From: Kaneshiro, Julie A
Sent: Tuesday, June 03, 2003 11:20 AM
To: Schwetz, Bernard A; Carome, Michael; Odwazny, Laura; Stith-Coleman, Irene; Higgins, Yvonne; Hicks, Shirley; Borrer, Kristina
Subject: RE: Follow-up on FDA's ANPRM on "IRB shopping"

Bern, I also recall Dave pointing out that there was little evidence of "IRB shopping" in FDA-regulated research. My initial thought is that such data collection might not be necessary given that our assurance process requires that institutions formally designate the IRB(s) that will be responsible for reviewing human subjects research conducted under the assurance-- and I believe most institutions have designated only one IRB. (Yvonne, please correct me if I'm wrong about this.) However, it seems that "IRB shopping" could occur in institutions that have designated more than one IRB to review its research. In such cases, OHRP might not necessarily know if "IRB shopping" was occurring between the institution's designated IRBs, but I suspect this happens very rarely, if ever.

What do others think about the need for OHRP to collect data on this issue? In OHRP's experience, has "IRB shopping" been an issue for us? Thanks for your thoughts.

Julie

-----Original Message-----

From: Schwetz, Bernard A
Sent: Monday, June 02, 2003 12:15 PM
To: Kaneshiro, Julie A; Carome, Michael; Odwazny, Laura; Stith-Coleman, Irene
Subject: RE: Follow-up on FDA's ANPRM on "IRB shopping"

Julie--do I recall correctly that Dave pointed out that there is little or no evidence of "IRB shopping" and questioned whether this is high enough priority to do anything? It seems to me that we should take some step to address the recommendation and that we should do it together with the FDA if we can. Do we need to more formally collect some data as the basis for any action, especially if we say this appears to not be a problem and we are not going to do anything further for now? Bern

-----Original Message-----

From: Kaneshiro, Julie A
Sent: Monday, June 02, 2003 12:00 PM
To: Schwetz, Bernard A; Carome, Michael; Odwazny, Laura; Stith-Coleman, Irene
Subject: Follow-up on FDA's ANPRM on "IRB shopping"

At our meeting with FDA last Friday, you'll recall that Dave asked whether OHRP would like to issue a joint letter with FDA to the IG regarding the public comments FDA received on its ANPRM on "IRB shopping." After reviewing our response to the

IG from 1998, I think this would be useful. Here's some background in case it's helpful:

You may recall that in 1998, the IG issued a report entitled, "Institutional Review Boards: A Time for Reform." In this report, the IG recommended that NIH/OPRR and FDA should "require sponsors and investigators to notify IRBs of any prior IRB review of a research plan." Importantly, in NIH's/OPRR's formal response to the IG report, we stated that "OPRR will work with the FDA to define standards for informing IRBs of prior negative reviews by IRBs."

FDA subsequently issued an ANPRM in March 2002, requesting public comments on whether the FDA should revise its IRB regulations to require sponsors and investigators to inform IRBs about any prior IRB review decisions. From a conversation I had with Phil Chao a couple of months ago, I believe the comments in favor of such a change were very general, while the comments opposed were numerous and raised many specific concerns as to why this should not be done.

To my knowledge, however, OPRR/OHRP has not pursued this issue, so there would probably be value to us in joining FDA's response to the IG (depending on what FDA decides to say). While some of the issues raised by commenters on FDA's ANPRM are likely to have been specific to the FDA's IRB regulations, we may be able to craft a letter that addresses the issue more broadly. In any case, it would probably be useful to pursue this with FDA to see if this would be feasible. Just let me know if you'd like me to work with FDA on this.

Julie

OHRP-Approved FWAs

Year	Total Approved
2004	3456
2005	3555
2006	4318
2007	4397
2008	4143
1/09-2/09	892

year	# for-cause evaluations of FWAs opened	# not-for-cause evaluations of FWAs opened	# of FWA suspensions	# of FWA restrictions	reason for suspension or restriction
2008	8	3	0		
2007	16	4	2		1) HSR without an FWA or IRB review; 2) inadequate expertise or staff. inadequate review
2006	15	4			
2005	43	4	1		failure to conduct continuing review or have written IRB procedures
2004	16	3		1	inadequate review of research, particularly involving children

NOTE: OHRP only conducts evaluations of FWAs and designated IRBs; and only has authority to suspend/restrict FWAs

Abbreviations: HSR- human subjects research
 FWA- Federalwide Assurance
 IRB- institutional review board

OHRP conducted an analysis of 235 compliance oversight determination letters issued to 146 institutions between August 1, 2002 and August 31, 2007. The data from this analysis follow:

Table 1: Percentage of Institutions ($N = 146$) Cited by OHRP for Various Noncompliance and Deficiencies (08/2002-08/2007)

Percentage of Institutions (N=146) Cited by OHRP for Various Noncompliance and Deficiencies		
Category of Deficiency	# of Institutions Cited	% of Institutions Cited
IRB initial review process	82	56%
IRB-approved informed consent documents/process	75	51%
IRB continuing review process	32	22%
Written IRB policies and procedures	29	20%
IRB records, including IRB minutes	23	16%
IRB membership	9	6%
IRB review of protocol changes	35	24%
IRB expedited review procedure	22	15%
Reporting requirements	22	15%
Research conducted without IRB approval	25	17%
Application of exempt categories of research	4	3%
Failure to obtain informed consent of subjects	21	14%
Documentation of informed consent	12	8%
IRB members lack sufficient understanding of regulations	3	2%
IRB meeting space, staff, and resources	1	1%
Overburdened IRB	0	0%

Table 2: Distribution of OHRP Citations of Noncompliance and Deficiencies (08/2002-08/2007)

Category of Deficiency	# of Citations	% of Citations
IRB initial review process	153	20%
IRB-approved informed consent documents/process	260	34%
IRB continuing review process	37	5%
Written IRB policies and procedures	113	15%
IRB records, including IRB minutes	31	4%
IRB membership/training/support/workload	13	2%
IRB review of protocol changes	40	5%
IRB expedited review procedure	26	3%
Reporting requirements	24	3%
Research conducted without IRB approval	24	3%
Failure to obtain informed consent of subjects	19	2%
Other miscellaneous deficiencies	22	3%
Total	762	100%

Table 3: Distribution of OHRP Citations of Noncompliance and Deficiencies Related to Initial IRB Review (08/2002-08/2007)

Distribution of OHRP Citations of Noncompliance and Deficiencies Related to Initial IRB Review		
Area of Noncompliance or Deficiency in initial IRB review	# of Citations	% of Citations
Findings for research involving children	27	18%
Criteria for IRB approval	93	61%
Findings for waiver of IC requirements	12	8%
Contingent approval with substantive changes or clarification w/o further review by convened IRB	8	5%
IRB quorum requirements	4	3%
Review of federal grant applications	4	3%
Findings for research involving prisoners	1	1%
*Other Miscellaneous	4	3%
Total Citations of Noncompliance or Deficiency in Initial IRB Review	153	100%

Table 4: Distribution of OHRP Citations of Noncompliance and Deficiencies Related to Informed Consent (08/2002-08/2007)

Distribution of OHRP Citations of Noncompliance and Deficiencies Related to Informed Consent

Area of Noncompliance or Deficiencies Related to Informed Consent	# of Citations	% of Citations
Description of purpose, procedures, and duration	65	23%
Description of risks and discomforts	63	23%
Description of benefits	10	4%
Description of alternatives	35	13%
Description of other elements of informed consent	19	7%
Complexity of informed consent language	45	16%
Use of exculpatory language	5	2%
Other Miscellaneous	5	2%
Failure to obtain legally effective informed consent	19	7%
Documentation of informed consent	13	5%
TOTAL	279	100%

For the reasons discussed above, I certify that the proposed regulation:

1. Is not a "significant regulatory action" under Executive Order 12866;
2. Is not a "significant rule" under the DOT Regulatory Policies and Procedures (44 FR 11034, February 26, 1979); and
3. Would not have a significant economic impact, positive or negative, on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

We prepared a summary of the costs to comply with this proposal and placed it in the AD Docket. You may get a copy of this summary at the address listed under ADDRESSES.

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

The Proposed Amendment

Under the authority delegated to me by the Administrator, the Federal Aviation Administration proposes to amend 14 CFR part 39 as follows:

PART 39—AIRWORTHINESS DIRECTIVES

1. The authority citation for part 39 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701.

§ 39.13 [Amended]

2. Section 39.13 is amended by removing Amendment 39-13183 (68 FR 33621, June 5, 2003) and by adding the following new airworthiness directive:

International Aero Engines AG (IAE): Docket No. 2003-NE-21-AD.

Comments Due Date

(a) The Federal Aviation Administration (FAA) must receive comments on this airworthiness directive (AD) action by March 20, 2006.

Affected ADs

(b) This AD supersedes AD 2003-11-23, Amendment 39-13183.

Applicability

(c) This AD applies to International Aero Engines AG (IAE) V2522-A5, V2524-A5, V2527-A5, V2527E-A5, V2527M-A5, V2530-A5, and V2533-A5 turbofan engines with engine serial numbers V10600 through V11365 and bearings P/N 2A1165 installed. These engines are installed on, but not limited to, Airbus Industrie A319, A320, and A321 series airplanes.

Unsafe Condition

(d) This AD results from reports of No. 3 bearing failures that caused in-flight shutdown (IFSD) and smoke in the cockpit and cabin. We are issuing this AD to prevent failure of the No. 3 bearing, which could result in an IFSD and smoke in the cockpit and cabin.

Compliance

(e) You are responsible for having the actions required by this AD performed within the compliance times specified unless the actions have already been done.

Inspection of the Master Magnetic Chip Detector (MCD) or the No. 1, 2, 3 Bearing Chamber MCD

(f) For engines listed in Appendix 1, Tables 1 and 2 of IAE service bulletin (SB) V-2500-ENG-72-0452, Revision 3, dated March 4, 2005, and that have a No. 3 bearing, part number (P/N) 2A1165, installed at new production build, do the following:

(1) Within 125 hours time-in-service (TIS) after the effective date of this AD, inspect the master MCD or the No. 1, 2, 3 bearing chamber MCD.

(2) Thereafter, within 125 hours time-since-last inspection, inspect the master MCD or the No. 1, 2, 3 bearing chamber MCD.

(3) If you find bearing material on the master MCD or No. 1, 2, 3 bearing chamber MCD, replace the engine before further flight.

Replacement of No. 3 Bearing

(g) For engines listed in Appendix 1, Tables 1 and 2 of IAE SB V-2500-ENG-72-0459, Revision 2, dated March 4, 2005, that have a serial number (SN) from V10600 through V11365 inclusive, and that have a No. 3 bearing, part number (P/N) 2A1165, installed at new production, replace the No. 3 bearing at the next shop visit for any reason.

(h) After the effective date of this AD, do not install any No. 3 bearing, P/N 2A1165, removed in paragraph (g) of this AD, into any engine.

Replacement or Rework of High Pressure Compressor (HPC) Stubshaft

(i) For engines listed in Appendix 1, Tables 1 and 2 of IAE SB V-2500-ENG-72-0459, Revision 2, dated March 4, 2005, that have a SN from V10600 through V11365 inclusive, at the next shop visit for any reason, replace the HPC stubshaft that has a low-energy plasma coating with an HPC stubshaft that has a high-energy plasma coating.

Terminating Action

(j) Performing the requirements specified in paragraphs (g) and (i) of this AD is terminating action to the repetitive MCD inspections specified in paragraph (f)(1) through (f)(3) of this AD.

Alternative Methods of Compliance (AMOCs)

(k) The Manager, Engine Certification Office, has the authority to approve alternative methods of compliance for this AD if requested using the procedures found in 14 CFR 39.19.

Material Incorporated by Reference

(l) For lists identifying engines within the engine SN range of V10600 to V11365 inclusive, known to have had P/N 2A1165 installed, you must use Appendix 1, Tables 1 and 2 of IAE SB V-2500-ENG-72-0452, Revision 3, dated March 4, 2005, and IAE SB V-2500-ENG-72-0459, Revision 2, dated March 4, 2005.

Related Information

(m) The following service bulletins contain additional information and procedures:

(1) You can find information on inspecting the master MCD and the No. 1, 2, 3 bearing chamber MCD in section 79-00-00-601 of the Aircraft Maintenance Manual.

(2) Additional information on inspection procedures is included in IAE SB V-2500-ENG-72-0452, Revision 3, dated March 4, 2005.

(3) You can find information on replacing the No. 3 bearing, and replacing or recoating the HPC stubshaft in IAE SB V-2500-ENG-72-0459, Revision 2, dated March 4, 2005.

Issued in Burlington, Massachusetts, on January 9, 2006.

Peter A. White,

Acting Manager, Engine and Propeller Directorate, Aircraft Certification Service.

[FR Doc. E6-379 Filed 1-13-06; 8:45 am]

BILLING CODE 4910-13-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 56

[Docket No. 2001N-0322 (formerly 01N-0322)]

Institutional Review Boards: Requiring Sponsors and Investigators to Inform Institutional Review Boards of Any Prior Institutional Review Board Reviews; Withdrawal

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking; withdrawal.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal of an advance notice of proposed rulemaking (ANPRM) entitled "Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews" that published in the Federal Register of March 6, 2002 (67 FR 10115).

DATES: The ANPRM is withdrawn February 16, 2006.

FOR FURTHER INFORMATION CONTACT: Patricia M. Beers Block, Good Clinical Practice Program (HF-34), Food and Drug Administration, 5600 Fishers Lane, rm. 9C24, Rockville, MD 20857, 301-827-3340.

SUPPLEMENTARY INFORMATION: In 1998, the Department of Health and Human Services, Office of the Inspector General (OIG) issued several reports on institutional review boards (IRBs). The OIG sought to identify the challenges facing IRBs and to make recommendations on improving Federal

oversight of IRBs. One recommendation was that sponsors and clinical investigators be required to notify IRBs of any prior review (see OIG, Department of Health and Human Services, "Institutional Review Boards: A Time for Reform," p. 14, June 1998; <http://oig.hhs.gov/oei/reports/oei-01-97-00193.pdf>). The OIG report stated that the OIG had:

* * * heard of a few situations where sponsors and/or research investigators who were unhappy with one IRB's reviews switched to another without the new IRB being aware of the other's prior involvement. This kind of IRB shopping deprives the new IRB of information that it should have and that can be important in protecting human subjects. The ground rules should be changed so that sponsors and investigators have the clear obligation to inform an IRB of any prior reviews (footnote omitted). The obligation should be applied to all those conducting research funded by HHS or carried out on FDA-regulated products. It will have particular importance for those sponsors and investigators working with independent IRBs.

Id.
After reviewing the OIG's recommendation, FDA published an ANPRM on March 6, 2002 (67 FR 10115) (see <http://www.fda.gov/OHRMS/DOCKETS/98fr/030602a.pdf>) announcing it was considering whether to amend its IRB regulations to require sponsors and investigators to inform IRBs about any prior IRB review decisions. We invited public comments on: (1) The frequency of IRB shopping and under what circumstances IRB shopping has occurred; (2) what information about prior IRB review should be disclosed, where should it be disclosed, and who should disclose it; and (3) what methods, other than disclosure of prior IRB reviews, might prove to be valuable for dealing with IRB shopping.

In response to this ANPRM, FDA received 55 comments. The majority of the comments reported they had little or no first hand knowledge of instances of IRB shopping, and did not believe IRB shopping presented a significant problem. Many comments expressed concern about the logistics of maintaining a system that would enable the exchange of information among IRBs, especially when studies involved multiple study sites. There was concern that maintaining such a system would substantially increase the IRBs' workload and not provide any additional human subject protection. There was also concern that waiting for information from other IRBs prior to the review of research proposals within a particular institution might contribute to delays in the review of these proposals.

The Office of Human Research Protections (OHRP) also informed FDA that it considered the OIG's recommendation to require sponsors and investigators to notify IRBs of any prior IRB review of a research plan. OHRP concluded that it had no reason to believe that IRB shopping was occurring with any regularity in the review of HHS conducted or supported human subjects research.

Based on these reasons, FDA concluded that IRB shopping either does not occur or does not present a problem to an extent that would warrant rulemaking at this time.

In a letter dated February 26, 2005, FDA advised the OIG of these findings and conclusions. FDA is now withdrawing this ANPRM. A withdrawal does not prevent the agency from taking action in the future. Should FDA decide to undertake rulemaking sometime in the future, the agency will provide new opportunities for comment.

Dated: January 4, 2006.
Jeffrey Shuren,
Assistant Commissioner for Policy.
[FR Doc. E6-357 Filed 1-13-06; 8:45 am]
BILLING CODE 4180-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 210

[Docket No. 2005N-0285]

Current Good Manufacturing Practice Regulation and Investigational New Drugs; Companion Document to Direct Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is publishing this companion proposed rule to the direct final rule, published elsewhere in this issue of the *Federal Register*, which is intended to amend our current good manufacturing practice (CGMP) regulations for human drugs, including biological products, to exempt most investigational "Phase 1" drugs from complying with the regulatory requirements. We will instead exercise oversight of production of these drugs under the agency's general statutory CGMP authority and investigational new drug application (IND) authority. Elsewhere in this issue of the *Federal Register*, FDA is announcing the availability of a draft guidance for

industry entitled "INDs—Approaches to Complying With CGMP During Phase 1" to provide further guidance on the subject.

DATES: Submit written or electronic comments by April 3, 2006.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/comments>.

FOR FURTHER INFORMATION CONTACT: Monica Caphart, Center for Drug Evaluation and Research (HFD-320), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-9047; or Christopher Joneckis, Center for Biologics Evaluation and Research (HFM-1), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-435-5681.

SUPPLEMENTARY INFORMATION:

I. Background

As described more fully in the related direct final rule, a Phase 1 clinical trial includes the initial introduction of an investigational new drug into humans. Such studies are aimed at establishing basic safety and are designed to determine the metabolism and pharmacologic actions of the drug in humans. The total number of subjects in a Phase 1 study is limited—generally no more than 80 subjects. This is in contrast to Phase 2 and Phase 3 trials, which may involve substantially greater numbers of subjects, exposing more subjects to the drug product, and which aim to test the effectiveness of the drug product.

For several reasons, we believe that production of human drug products, including biological drug products, intended for use in Phase 1 clinical trials should be exempted from complying with the specific regulatory requirements set forth in parts 210 and 211 (21 CFR parts 210 and 211). First, even if exempted from the requirements of our CGMP regulations in parts 210 and 211, investigational drugs remain subject to the statutory provisions that deem a drug adulterated for failure to comply with CGMPs (21 U.S.C. 351(a)(2)(B)).

Second, we oversee drugs for use in Phase 1 trials through our existing IND authority. Every IND must contain, among other things, a section on chemistry, manufacturing, and control information that describes the composition, manufacture, and control of the investigational drug product (21 CFR 312.23(a)(7)). This information should suffice to enable us to

Coast IRB Revenue: 2005-2008

2005	\$4,408,397
2006	\$5,622,023
2007	\$7,208,058
2008	\$9,325,485

Submission Number: 10715
Institution Name: DEVICE MED-SYSTEMS
OMB No. 0990-0278
Approved for use through 1/31/2008

3/25/2008 2:39:49 PM

U.S. Department of Health and Human Services (DHHS)
Federalwide Assurance (FWA) for the Protection of Human Subjects
For Domestic (U.S.) Institutions

1. Institution Filing Assurance

Legal Name: DEVICE MED-SYSTEMS
City: CLIFTON State: VA

HHS Institutional Profile Code:
Federal Entity Identification Number (EIN): 26-2238523
This Assurance replaces:

2. Institutional Components

List below all components over which the institution has legal authority that operate under a different name. Also list with an asterisk (*) any alternate names under which the institution operates. The institution should have available for review by the Office for Human Research Protections (OHRP) upon request a brief description and line diagram explaining the interrelationships among the Assurance Signatory Official, the Institutional Review Board (IRB), IRB support staff, and investigators in these various components.

NOTE: The Signatory Official signing this Assurance must be legally authorized to represent the institution providing this Assurance and all components listed below. Entities that the Signatory Official is not legally authorized to represent may not be listed here without the prior approval of OHRP.

None Selected

3. Statement of Principles

This institution assures that all of its activities related to human subjects research, regardless of funding source, will be guided by the ethical principles in the following documents:

THE BELMONT REPORT

Submission Number: 10715
 Institution Name: DEVICE MED-SYSTEMS
 OMB No. 0990-0278
 Approved for use through 1/31/2008

3/25/2008 2:39:48 PM

4. Applicability

(a) This Institution assures that whenever it engages in human subjects research conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule, the institution will comply with the Terms of the Federawide Assurance for Institutions Within the United States (contained in a separate document on the OHRP website), unless the research is otherwise exempt from the requirements of the Common Rule or a department or agency conducting or supporting the research has determined that the research shall be covered by a separate assurance.

(b) Optional: This Institution elects to apply the following to all of its human subjects research regardless of the source of support, except for research that is covered by a separate assurance:

The Common Rule and subparts B, C, and D of the HHS regulations at 45 CFR part 46

5. Designation of Institutional Review Boards (IRBs)

This institution designates the following IRB(s) for review of research under this Assurance (if the IRB has not previously registered with HHS or has not provided a membership roster to HHS, please submit to OHRP the appropriate IRB registration materials which are available on the OHRP website).

NOTE: Reliance on the IRB of another institution or organization or an independent IRB must be documented by a written agreement that is available for review by OHRP upon request. OHRP's sample IRB Authorization Agreement may be used for this purpose, or the parties involved may develop their own agreement. Future designation of other IRBs requires an update of the FWA.

HHS IRB Registration Number	Name of IRB As Registered with HHS
IRB00006417	MARYLAND HAUSE IRB IRB #1 - MARYLAND HAUSE

Submission Number: 10715

3/25/2008 2:38:49 PM

Institution Name: DEVICE MED-SYSTEMS

OMB No. 0990-0278

Approved for use through 1/31/2008

6. Human Protections Administrator (e.g., Human Subjects Administrator or Human Subjects Contact Person)

First Name: PAUL

Middle Initial: M

Last Name: JENNINGS

Degrees or Suffix (e.g., MD, PhD): PH.D.

Institutional Title: PRESIDENT/HUMAN PROTECTIONS ADMINISTRATOR

Institution: DEVICE MED-SYSTEMS

Telephone: (410) 916-3795

FAX:

E-mail: DEVICEMEDSYSTEMS@YAHOO.COM

Address: 5746 UNION MILL ROAD

City: CLIFTON

State: VA

Zip Code: 20124

2024123086

GAO 4271

02:04:25 p.m. 04-21-2008

1/1

IC/Bm 4/21
3/25/2008 2:39:49 PM

Submission Number: 10715
Institution Name: DEVICE MED-SYSTEMS
OMB No. 0990-0278
Approved for use through 1/31/2008

7. Signatory Official (i.e., Official Legally Authorized to Represent the Institution
-- cannot be IRB Chairperson or IRB member)

I understand that the Assurance Training Modules on the OHRP website describe the responsibilities of the Signatory Official, the IRB Chair(s), and the Human Protections Administrator under this Assurance. Additionally, I recognize that providing research investigators, IRB members and staff, and other relevant personnel with appropriate initial and continuing education about human subject protections will help ensure that the requirements of this Assurance are satisfied.

Acting officially in an authorized capacity on behalf of this Institution and with an understanding of the institution's responsibilities under this Assurance, I assure protections for human subjects as specified above. The IRB(s) designated above are to provide review for all research to which this Assurance applies. The designated IRB(s) will comply with the Terms of the Federalwide Assurance for Institutions Within the United States and possess appropriate knowledge of the local context in which this Institution's research will be conducted.

All information provided with this Assurance is up-to-date and accurate. I am aware that false statements could be cause for invalidating this Assurance and may lead to other administrative or legal action.

Signature: Richard N. Shelton Date: 3/26/08

Richard N Shelton

First Name: RICHARD Middle Initial: N Last Name: SHELTON
Degrees or Suffix (e.g., MD, PhD): PH.D. Institutional Title: CEO
Institution: DEVICE MED-SYSTEMS
Telephone: (410) 916-3795 FAX: E-mail:
Address: 5746 UNION MILL ROAD
City: CLIFTON State: VA Zip Code: 20124

NOTE: Institutions operated by the U.S. Government may need to obtain department or agency clearance prior to submission of the FWA to OHRP. Please contact the relevant department or agency Human Subject Protections Officer before forwarding this Assurance to OHRP.

Submission Number: 10715
Institution Name: DEVICE MED-SYSTEMS
OMB No. 0990-0278
Approved for use through 1/31/2008

3/25/2008 2:39:49 PM

8. FWA Approval

The Federalwide Assurance for the Protection of Human Subjects for Institutions Within the United States submitted to HHS by the above Institution is hereby approved.

Assurance Number: FWA 000 13107 Expiration Date: 4-21-2011
Signature of HHS Approving Official: Irene Stich-Coleman Date: 21 April 08
Director, DPA, OHRP

Public burden for this collection of information is estimated to average two hours for a new FWA filing and less than an hour for an FWA renewal or update. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: OS Reports Clearance Officer, Room 503, 200 Independence Avenue, SW., Washington, DC 20201. Do not return the completed form to this address.

Submission Number: 10715
Institution: DEVICE MED-SYSTEMS

NOTES HISTORY

4/21/2008 4:53:26 PM Irene S
New FWA; optionally selected, under 4b, to apply all parts of 45 CFR 46 to all research.

StithColeman, Irene E (HHS/OPHS)

From: StithColeman, Irene E (HHS/OPHS)
Sent: Monday, April 21, 2008 4:55 PM
To: devicemedsystems@yahoo.com; devicemedsystems@yahoo.com
Cc: StithColeman, Irene E (HHS/OPHS)
Subject: Electronic FWA Application for Device Med-Systems Approved by OHRP as FWA00013107

This is an automated message from an unmonitored address. Please do not reply.

Your institution's electronic submission of a Federalwide Assurance (FWA) has been approved by the Office for Human Research Protections (OHRP), and the FWA number assigned to your institution, Device Med-Systems, is FWA00013107. You will find this approval listed on our website at <http://ohrp.cit.nih.gov/search/asearch.asp#ASUR>. Funding agencies use this website to verify that an institution holds an active OHRP-approved FWA.

Whenever information provided to OHRP changes for your institution's FWA, you must submit an update/renewal. You may do this electronically by going to the OHRP Electronic Submission System at <http://ohrp.cit.nih.gov/efile/>. Your FWA must be renewed at least every 3 years.

Effective February 1, 2005, OHRP stopped mailing copies of approved Federalwide Assurance (FWA) documents to filing institutions. This was necessitated by the volume of FWA documents OHRP is managing. Over 10,000 FWAs have been approved. OHRP encourages FWA institutions to continue to submit documents (new and updates/renewals) electronically (<http://ohrp.cit.nih.gov/efile/>). When an electronic submission is processed, an automatically generated e-mail notifies the Human Protections Administrator and Signatory Official, as well as the person submitting the electronic record, that the FWA document has been approved. This, of course, is dependent upon the electronic file submitted to OHRP providing e-mail addresses as requested.

Sincerely,

Division of Policy and Assurances
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
(240) 453-6900
Toll-Free within the U.S. (866) 447-4777

FWA Submission Number: 10715

4/21/2008 4:52:43 PM

Device Med-Systems

Signatory Official:

Richard N Shelton Ph.D.

IRB LINKS

IRB #: IRB00006417

IRB Name: Maryland Hause IRB IRB #1 - Maryland Hause

Last Update: 2/27/2008

Chairperson: John J Wilson PhD

IORG #: IORG0005335

IORG Name: Maryland Hause IRB

Expires: 2/27/2011

SOFCTH
JSC
21 April 08

ASUR Number: FWA00013107
Institution: DEVICE MED-SYSTEMS
Expires: 4/21/2011

TRANSACTION HISTORY

4/21/2008 4:54:43 PM Irene S
Approved Electronic FWA

4/21/2008 2:28:13 PM Bill M
Edit Log Record

4/21/2008 2:28:12 PM Bill M
Edit Log Record

4/21/2008 2:28:11 PM Bill M
Signature Page Received (Initial)

4/21/2008 2:28:10 PM Bill M
Edit Log Record

3/25/2008 2:39:26 PM E-Submitter
Electronic Submission

IORG Number: IORG0005726

Renewal Date: 2/9/2012

Status: ACTIVE

U.S. Department of Health and Human Services (DHHS)
Institutional Review Board / Independent Ethics Committee Registration

1. Organization Operating the IRB(s)

Name of Organization: E-Z REVIEWS, INC.

Mailing Address: 1234 PHULOVIT LANE SE

Street Address:

City: CHETESVILLE

State: ARIZONA

Zip Code: 86028

*2/9/04
CP*

2. Head Official of Organization Operating the IRB(s)

First Name: DONALD

Middle Initial: M

Last Name: MCSPEED

Degrees or Suffix: III

Organizational Title: PRESIDENT

Institution: E-Z REVIEWS, INC.

Telephone: 928 561-2234

Fax:

E-Mail: EZREVIEWSINC@YAHOO.COM

Mailing Address: 1234 PHULOVIT LANE SE

Street Address:

City: CHETESVILLE

State: ARIZONA

Zip Code: 86028

3. Person Providing This Information

First Name: TIMOTHY

Middle Initial: J

Last Name: WITLESS

Degrees or Suffix:

Organizational Title: VICE PRESIDENT

Telephone: 928 561-2234

Fax:

E-Mail: EZREVIEWSINC@YAHOO.COM

IRB # IRB00006904

Renewal Date: 2/9/2012

Status: ACTIVE

E-Z Reviews, Inc. IRB #1

Accrediting Organization:

Approximate total number of currently active protocols: SMALL (1-25)

Approximate number of full time positions devoted to this IRB's administrative activities: 3

Does the IRB review, or intend to review, research supported by the US Govt? YES

Approximate number of currently active protocols supported by DHHS: NONE

Approximate number of currently active protocols supported by other Federal Agencies: NONE

Does the IRB review, or intend to review, FDA-regulated research? YES

Approximate number of currently active protocols involving FDA-regulated products: NONE

Currently active FDA-regulated protocols involve:

IRB Chairperson

First Name: ALAN

Middle Initial: P

Last Name: RUSE

Degrees or Suffix: PHD

Organizational Title: CHAIRMAN

Telephone: 928 561-2234

Fax:

E-Mail: EZREVIEWSINC@YAHOO.COM

Mailing Address: 1234 PHULOVIT LANE SE

Street Address:

City: CHETESVILLE

State: ARIZONA

Zip Code: 86028

IRB Number: IRB00006904
Roster Updated: 2/9/2009
Renewal Date: 2/9/2012

E-Z REVIEWS, INC. IRB #1
MEMBER ROSTER

VOTING MEMBERS

Mem #	Name	Gender	Affiliated?	Scientist?	Degree	Specialty
1	(Chair) RUSE, ALAN	M	N	Y	PhD	Behavioral Science
2	JOHNSON, TITO	M	Y	Y	MD	Cardiology
3	RIPLEY, HELEN	F	N	N	MBA	Business
4	PHULS, APRIL	F	N	Y	MD	Neuropathology
5	ANDERSON, JACK	M	N	N	PhD	Ethics
6	POWERS, MAX	M	N	N	MBA	Finance

2/9/2009 3:06:14 PM

Anderson, Charmaine (HHS/OPHS)

From: Anderson, Charmaine (HHS/OPHS)
Sent: Monday, February 09, 2009 3:06 PM
To: EZreviewsinc@yahoo.com; EZreviewsinc@yahoo.com;
 EZreviewsinc@yahoo.com
Cc: Anderson, Charmaine (HHS/OPHS)
Subject: Electronic IORG-IRB/IEC(s) Registration for E-Z Reviews, Inc. Processed by OHRP as IORG0005726

This is an automated message from an unmonitored address. Please do not reply.

The registration submitted electronically for your institutional review board/institutional ethics committee (IRB/IEC) organization (IORG) has been processed and assigned IORG0005726. The IORG number represents the overall registration, with each IRB/IEC receiving a distinct identification number. The expiration date for your institution's IORG registration is 2/9/2012. The following IRB/IEC(s) are registered with the Office for Human Research Protections (OHRP):

IRB00006904 E-Z Reviews, Inc. IRB #1

This registration is listed on our website at <http://ohrp.cit.nih.gov/search/asearch.asp#ASUR>. Funding agencies use this website to verify that an institutional review board/independent ethics committee (IRB/IEC) has an active registration.

Whenever information provided to OHRP changes for this IORG-IRB/IEC registration, your organization must submit an update/renewal. You may do this electronically by going to the OHRP Electronic Submission System at <http://ohrp.cit.nih.gov/efile/>. The IORG-IRB/IEC registration must be renewed at least every 3 years.

OHRP encourages organizations to continue to submit IORG-IRB/IEC registration documents electronically (<http://ohrp.cit.nih.gov/efile/>). When an electronic submission is processed, an automatically generated e-mail notifies the person submitting the electronic record, the Information Provider, the Chair(s) of the IRB/IEC(s), and the Head Official on the IRB/IEC registration that the document has been processed. This, of course, is dependent upon the electronic file submitted to OHRP providing e-mail addresses as requested.

Sincerely,

Division of Policy and Assurances
 Office for Human Research Protections
 U.S. Department of Health and Human Services
 1101 Wootton Parkway, Suite 200
 Rockville, MD 20852
 (240) 453-6900
 Toll-Free within the U.S. (866) 447-4777



DOCUMENT LOG | IRB REGISTRY | ASSURANCE REGISTRY | QIP | UTILITIES | EXIT HATS |

IRB Registry - Linked Assurances

- ▶ IRB
- ▶ Linked Assurances
- ▶ Chairperson
- ▶ Membership
- ▶ IRB Notes
- ▶ IRB History
- IRB List

IORG0005726 E-Z Reviews, Inc.

IRB00006904 E-Z Reviews, Inc. IRB #1

ASSURANCE NAME	ASSURANCE #	STATUS OF LINK	DATE
Phaké Med Devices, Inc.	FWA00014102	ACTIVE	02/10/2009

IORG Number: IORG0005726
Institution: E-Z REVIEWS, INC
Expires: 2/9/2012

TRANSACTION HISTORY

2/9/2009 3:06:12 PM Charmaine
Approved Electronic IORG

2/9/2009 11:33:35 AM Bill M
Edit Log Record

2/9/2009 11:33:34 AM Bill M
Edit Log Record

2/3/2009 2:59:50 PM E-Submitter
Electronic Submission

Submission Number: 11995

2/9/2009 3:44:16 PM

Institution Name: PHAKE MEDICAL DEVICES, INC.

OMB No. 0990-0278

Approved for use through May 31, 2011

U.S. Department of Health and Human Services (DHHS)
Federalwide Assurance (FWA) for the Protection of Human Subjects
For Domestic (U.S.) Institutions

1. Institution Filing Assurance

Legal Name: PHAKE MEDICAL DEVICES, INC.

City: PAYNESVILLE

State: SC

HHS Institution Profile File (IPF) code, if known:

Federal Entity Identification Number (EIN), if known:

If this Assurance replaces an MPA or CPA, please provide the 'M' or 'T' number:

2. Institutional Components

List below all components over which the institution has legal authority that operate under a different name. Also list with an asterisk (*) any alternate names under which the institution operates. The institution should have available for review by the Office for Human Research Protections (OHRP) upon request a brief description and line diagram explaining the interrelationships among the Assurance Signatory Official, the Institutional Review Board(s) (IRB), IRB support staff, and investigators in these various components.

NOTE: The Signatory Official signing this Assurance must be legally authorized to represent the institution providing this Assurance and all components listed below. Entities that the Signatory Official is not legally authorized to represent may not be listed here without the prior approval of OHRP.

None Selected

3. Statement of Principles

This institution assures that all of its activities related to human subjects research, regardless of the source of support, will be guided by the ethical principles in the following document(s): (indicate below)

THE BELMONT REPORT

Submission Number: 11995

2/9/2009 3:44:16 PM

Institution Name: PHAKÉ MEDICAL DEVICES, INC.

OMB No. 0990-0278

Approved for use through May 31, 2011

4. Applicability

(a) This Institution assures that whenever it engages in human subjects research conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule, the Institution will comply with the Terms of the Federalwide Assurance for Institutions Within the United States (contained in a separate document on the OHRP website), unless the research is otherwise exempt from the requirements of the Common Rule or a department or agency conducting or supporting the research has determined that the research shall be covered by a separate assurance.

(b) Optional: This Institution elects to apply the following to all of its human subjects research regardless of the source of support, except for research that is covered by a separate assurance:

The Common Rule and subparts B, C, and D of the HHS regulations at 45 CFR part 46

5. Designation of Institutional Review Boards (IRBs)

This Institution designates the following IRB(s) for review of research under this Assurance (if the IRB has not previously registered with HHS or has not provided a membership roster to HHS, please submit to OHRP the appropriate IRB registration materials which are available on the OHRP website).

NOTE: Reliance on the IRB of another institution or organization or an independent IRB must be documented by a written agreement that is available for review by OHRP upon request. OHRP's sample IRB Authorization Agreement may be used for this purpose, or the parties involved may develop their own agreement. Future designation of other IRBs requires an update of the FWA.

HHS IRB Registration Number	Name of IRB As Registered with HHS
IRB00006904	E-Z REVIEWS, INC. IRB #1

Submission Number: 5595

OMB No. 0990-0279

Approved for use through 1/31/2008

U.S. Department of Health and Human Services (DHHS)
Institutional Review Board / Independent Ethics Committee Registration

1. Organization Operating the IRB(s)

Name of Organization: MARYLAND HAUSE IRB

Mailing Address: 6030 DAYBREAK CIRCLE
SUITE 102

Street Address:

City: CLARKESVILLE

State: MD

New IORG # 000538
Date Processed 2/27/08 Initials: DA
Exp. Date: 2-27-11
ZIP CODE: 21029

2. Senior or Head Official of Organization Operating the IRB(s)

First Name: TRUPER

Middle Initial: W

Last Name: DAUG

Degrees or Suffix:

Organizational Title: PRESIDENT/ADMINISTRATOR

Institution: MARYLAND HAUSE IRB

Telephone: 571 220-2528

Fax:

E-Mail: MARYLANDHAUSEIRB@YAHOO.COM

Mailing Address: 6030 DAYBREAK CIRCLE
SUITE 102

Street Address:

City: CLARKESVILLE

State: MD

Zip Code: 21029

3. Person Providing This Information

First Name: RICHARD

Middle Initial: J

Last Name: RICKETTS

Degrees or Suffix:

Organizational Title: RESEARCH ADMINISTRATOR

Telephone: 571 220-2528

Fax:

E-Mail: MARYLANDHAUSEIRB@YAHOO.COM

Submission Number: 5595

MARYLAND HAUSE IRB IRB #1 - MARYLAND HAUSE MEMBER ROSTER

VOTING MEMBERS

Mem #	Name	Gender	Affiliated?	Scientist?	Degree	Specialty
1	(Chair) WILSON, JOHN	M	N	Y	PhD	Behavioral
2	BUTLER, JOHN	M	N	N	MD	Cardiology
3	FEATHERSTONE, WILLIAM	M	N	Y	PhD	Business
4	HOBSON, HENRY	M	Y	N	MD	Neuropathology
5	HUSSEIN, BEZLAN	F	N	Y	PhD	Ethics
6	DAUG, TRUPER	M	N	N	MBA	Business

Public burden for this collection of information is estimated to average one hour for an initial IRB registration or a complete update of an existing IRB registration and 30 minutes for a limited update of an IRB registration. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: OS Reports Clearance Officer, Room 503, 200 Independence Avenue, SW., Washington, DC 20201. Do not return the completed form to this address.

Submission Number: 11995

2/9/2009 3:44:16 PM

Institution Name: PHAKÉ MEDICAL DEVICES, INC.

OMB No. 0990-0278

Approved for use through May 31, 2011

6. Human Protections Administrator (e.g., Human Subjects Administrator or Human Subjects Contact Person)

First Name: VINCE

Middle Initial: N

Last Name: FEELGOOD

Degrees or Suffix (e.g., MD, PhD): MD

Institutional Title: PRESIDENT/HUMAN SUBJECTS ADMINISTRATOR

Institution: PHAKÉ MEDICAL DEVICES, INC.

Telephone: (843) 561-1646

FAX:

E-mail: PHAKEMED@YAHOO.COM

Address: 2232 WOUNDED LIMB DRIVE
SUITE #6

City: PAYNESVILLE

State: SC

Zip Code: 29915

Submission Number: 11895
Institution Name: PHAKÉ MEDICAL DEVICES, INC.
OMB No. 0890-0278
Approved for use through May 31, 2011

2/9/2009 3:44:16 PM

7. Signatory Official (i.e., Official Legally Authorized to Represent the Institution
— cannot be IRB Chairperson or IRB member)

I understand that the Assurance Training Modules on the OHRP website describe the responsibilities of the Signatory Official, the IRB Chair(s), and the Human Protections Administrator under this Assurance. Additionally, I recognize that providing research investigators, IRB members and staff, and other relevant personnel with appropriate initial and continuing education about human subject protections will help ensure that the requirements of this Assurance are satisfied.

Acting officially in an authorized capacity on behalf of this Institution and with an understanding of the Institution's responsibilities under this Assurance, I assure protections for human subjects as specified above. The IRB(s) designated above are to provide review for all research to which this Assurance applies. The designated IRB(s) will comply with the Terms of the Federawide Assurance for Institutions Within the United States and possess appropriate knowledge of the local context in which this Institution's research will be conducted.

All information provided with this Assurance is up-to-date and accurate. I am aware that false statements could be cause for invalidating this Assurance and may lead to other administrative or legal action.

Signature:  Date: 2-9-09
Douglas S Phaké

First Name: DOUGLAS Middle Initial: S Last Name: PHAKÉ
Degrees or Suffix (e.g., MD, PhD): ESQ. Institutional Title: CEO
Institution: PHAKÉ MEDICAL DEVICES, INC.
Telephone: (843) 561-1646 FAX: E-mail: PHAKEMED@YAHOO.COM
Address: 2232 WOUNDED LIMB DRIVE
SUITE #5
City: PAYNESVILLE State: SC Zip Code: 29915

NOTE: Institutions operated by the U.S. Government may need to obtain department or agency clearance prior to submission of the FWA to OHRP. Please contact the relevant department or agency Human Subject Protections Officer before forwarding this Assurance to OHRP.

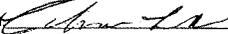
Submission Number: 11995
Institution Name: PHAKÉ MEDICAL DEVICES, INC.
OMB No. 0990-0278
Approved for use through May 31, 2011

2/9/2009 3:44:16 PM

8. FWA Approval

The Federalwide Assurance for the Protection of Human Subjects for Institutions Within the United States submitted to HHS by the above Institution is hereby approved.

Assurance Number: FWA 14108 Expiration Date: 2/10/2012

Signature of HHS Approving Official:  Date: 2/10/09

Charmaine L. Anderson
IRB/FWA Coordinator, OHRP

Public burden for this collection of information is estimated to average two hours for a new FWA filing and less than an hour for an FWA renewal or update. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: OS Reports Clearance Officer, Room 503, 200 Independence Avenue, SW., Washington, DC 20201. Do not return the completed form to this address.

Anderson, Charmaine (HHS/OPHS)

From: Anderson, Charmaine (HHS/OPHS)
Sent: Tuesday, February 10, 2009 12:56 PM
To: phakemed@yahoo.com; phakemed@yahoo.com; phakemed@yahoo.com
Cc: Anderson, Charmaine (HHS/OPHS)
Subject: Electronic FWA Application for Phaké Med Devices, Inc. Approved by OHRP as FWA00014102

This is an automated message from an unmonitored address. Please do not reply.

Your institution's electronic submission of a Federalwide Assurance (FWA) has been approved by the Office for Human Research Protections (OHRP), and the FWA number assigned to your institution, Phaké Med Devices, Inc., is FWA00014102. You will find this approval listed on our website at <http://ohrp.cit.nih.gov/search/asearch.asp#ASUR>. Funding agencies use this website to verify that an institution holds an active OHRP-approved FWA.

The expiration date for your FWA is 2/10/2012. Whenever information provided to OHRP changes for your institution's FWA, you must submit an update/renewal. You may do this electronically by going to the OHRP Electronic Submission System at <http://ohrp.cit.nih.gov/efile/>. Your FWA must be renewed at least every 3 years.

Effective February 1, 2005, OHRP stopped mailing copies of approved Federalwide Assurance (FWA) documents to filing institutions. This was necessitated by the volume of FWA documents OHRP is managing. Over 10,000 FWAs have been approved. OHRP encourages FWA institutions to continue to submit documents (new and updates/renewals) electronically (<http://ohrp.cit.nih.gov/efile/>). When an electronic submission is processed, an automatically generated e-mail notifies the Human Protections Administrator and Signatory Official, as well as the person submitting the electronic record, that the FWA document has been approved. This, of course, is dependent upon the electronic file submitted to RP providing e-mail addresses as requested.

Sincerely,

Division of Policy and Assurances
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
(240) 453-6900
Toll-Free within the U.S. (866) 447-4777

FWA Submission Number: 11995
Phaké Med Devices, Inc.
Signatory Official:
Douglas S Phaké Esq.

2/10/2009 12:55:17 PM

IRB LINKS

IRB #: IRB00006904
IRB Name: E-Z Reviews, Inc. IRB #1
Last Update: 2/9/2009
Chairperson: Alan P Ruse PhD
IORG #: IORG0005726
IORG Name: E-Z Reviews, Inc.
Expires: 2/9/2012

2/10/09
OR

ASUR Number: FWA00014102
Institution: PHAKÉ MED DEVICES, INC.
Expires: 2/10/2012

TRANSACTION HISTORY

2/10/2009 12:56:19 PM Charmaine
Approved Electronic FWA

2/10/2009 9:00:37 AM Bill M
Edit Log Record

2/10/2009 9:00:36 AM Bill M
Edit Log Record

2/10/2009 9:00:34 AM Bill M
Signature Page Received (Initial)

2/10/2009 9:00:33 AM Bill M
Edit Log Record

2/9/2009 3:44:11 PM E-Submitter
Electronic Submission

Dan Dueber

From: Diane Morrow [REDACTED]
Sent: Tuesday, March 17, 2009 9:36 AM
To: Dan Dueber
Cc: Diane Morrow; Jonathan Emord; Andrea Ferrenz
Subject: Re: Media Contacts

No word from Alicia still so I will try again. The NYT is a fickle group but let me check on a few things there as well. Will get back to you soon

Diane Morrow
Sent from my iPhone please forgive the typos

On Mar 17, 2009, at 9:43 AM, "Dan Dueber" <[REDACTED]> wrote:

Hi Diane --- any word from Alicia Mundy of the WSJ?

Also, I resent for the third or fourth time the letter to the editor of the NYT, and it still has not been published. Is there someone you can call and talk to about this? It feels like we are getting stonewalled.

Incredibly, I can't get our local paper to do a story on this. I emailed our two press releases to the Gazette, I know the reporter well, but that hasn't helped. So I emailed the press releases yesterday to the local Independent (alt. weekly) and the Colorado Springs Business Journal and haven't heard back from them yet.

It seems like this story has died and no one is interested any more. I was hoping we could keep the media pressure on this subcommittee so that perhaps they would decide to stay far away from me!

Tx Dan

Dan Dueber
President, CEO and Manager of LLC

Coast IRB, LLC | www.coastirb.com



510 | Registration & | Adverse | PMA | Classification | CLIA
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[Code of Federal Regulations]
 [Title 21, Volume 1]
 [Revised as of April 1, 2008]
 [CITE: 21CFR50.25]

TITLE 21--FOOD AND DRUGS
 CHAPTER I--FOOD AND DRUG ADMINISTRATION
 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 SUBCHAPTER A--GENERAL

PART 50 -- PROTECTION OF HUMAN SUBJECTS

Subpart B--Informed Consent of Human Subjects

Sec. 50.25 Elements of informed consent.

(a) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and

Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) 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.

(b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

Database Updated April 1, 2008

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Center for Devices and Radiological Health / CDRH



DEPARTMENT OF HEALTH & HUMAN SERVICES

58101
Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

MAR 11 2008

Certified Mail
Return Receipt Requested

Reference No. 08-HFD-45-1101

Darren McDaniel
Chief Executive Officer
Coast Institutional Review Board
5475 Mark Dabbling Blvd., Suite 351
Colorado Springs, CO 80918

Dear Mr. McDaniel:

Between July 10 and 18, 2007, Mr. James Fleckenstein, representing the Food and Drug Administration (FDA), inspected Coast IRB. The purpose of this inspection was to determine whether Coast IRB was in compliance with the regulations governing IRBs and those governing the protection of human subjects participating in clinical trials contained in Title 21 of the Code of Federal Regulations (CFR), Parts 56 and 50. These regulations apply to clinical investigations of products regulated by FDA. We are aware that at the conclusion of this inspection, our investigator presented and discussed with you a Form FDA 483, Inspectional Observations.

From our evaluation of the Form FDA 483, the establishment inspection report, the documents submitted with that report, and your written responses dated August 15 and November 29, 2007, we conclude that the IRB failed to adhere to certain requirements in 21 CFR Part 56 as described below. The regulatory violations were identified from the review of the IRB's written procedures and the review of the following study:

[] Protocol [] entitled "A Phase 1 Multi-Center, Open-Label, Randomized, 3-Arm Clinical Trial to Evaluate [] in the Treatment of []"

Page 2-Coast IRB

We wish to emphasize the following:

1. The IRB failed to follow FDA regulations regarding expedited review procedures [21 CFR 56.110(b)].

The regulations require that under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB, and the IRB may use the expedited review process to review either or both of the following: (1) some or all of the research appearing on the Federal Register list and found by the reviewer(s) to involve no more than minimal risk, or (2) minor changes in previously approved research during the period for which approval is authorized. Coast IRB's written procedures for expedited review also reflect this requirement. As explained below, Coast IRB had an inexperienced member conduct the expedited review and reviewed research under expedited review that did not meet the criteria above.

On March 19, 2007, you appointed Mr. [] to the IRB Board and instructed him to conduct an expedited review of the advertisement for the above referenced study. Mr. [] lacked the requisite relevant experience to conduct expedited review on behalf of the IRB. In addition, the advertisement reviewed under the expedited review procedure on March 19, 2007, did not qualify for expedited review under 21 CFR 56.110(b), as it was neither research appearing on the Federal Register list and found by the reviewer to involve no more than minimal risk nor minor changes to previously approved research. Finally, the advertisement was not appropriate for expedited review because the full IRB had met and reviewed it as discussed below.

The full IRB considered the recruitment advertisement for the study at three previously convened meetings on March 1, 8, and 15, 2007. On March 1, 2007, the IRB approved the advertisement with changes and that decision was communicated to the sponsor. Upon resubmission by the sponsor, the IRB disapproved the recruitment advertisement for the above study on both March 8 and 15, 2007. The initial approval with changes and the subsequent disapprovals were based on the IRB's determination that the advertisement was coercive in nature. In each case, the IRB or the IRB Chair proposed alternative language which would have been acceptable to the Board.

Despite the advertisement having been first approved with changes and then disapproved by the IRB, you appointed Mr. [] to the IRB Board on March 19, 2007, and then you directed Mr. [] to conduct an expedited review of the advertisement on that same day. On March 19, 2007, Mr. [] via expedited review, approved the advertisement in its original form which had previously been approved with changes and then disapproved as submitted by the full IRB. Despite the full board's consideration of this matter at three previous meetings, documentation of the disapprovals in the minutes of both March 8th and 15th, and e-mails that indicate otherwise, you stated that you were unaware of the Board's decisions on this matter.

Furthermore, the regulations at 21 CFR 56.110(b) require that the IRB chairperson conduct expedited review or designate an experienced reviewer to conduct an expedited review on behalf of the IRB. You, in your capacity as the chief executive officer of the IRB, lacked the authority to designate anyone to conduct expedited reviews on behalf of the IRB.

Page 3-Coast IRB

Your written response of August 15, 2007, acknowledges that expedited review may only be conducted by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. This written response also states that all advertisement/recruitment materials that underwent expedited review by Mr. [] are being reviewed by the Chair for regulatory compliance. Neither this written response nor your written response of November 29, 2007, addresses the issue that you directed review of the research under expedited review when it did not qualify under FDA regulations for expedited review and that you had Mr. [] conduct an expedited review despite Mr. [] lack of relevant experience.

- 2. The IRB did not follow written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and institution [21 CFR 56.108(a)(1) and 56.110(c)].**

As noted, the advertisement for the above referenced study was approved under an expedited review procedure. FDA's regulations require IRBs using an expedited review procedure to adopt a method for keeping all members advised of research proposals which have been approved under the procedure. Coast IRB's Standard Operating Procedure (SOP) Manual, Version 4, Section 4.1.1, stated that all regular members of the IRB were to be informed of such actions via the Coast IRB agenda. However, IRB members interviewed by FDA could not recall being notified about the expedited review and we were not able to locate an agenda with this expedited review listed as an agenda item. If Coast IRB has documentation notifying the IRB members about this expedited review, please provide it.

- 3. The IRB did not maintain minutes of meetings in sufficient detail to indicate the actions taken by the IRB [21 CFR 56.115(a)(2)].**

The minutes for the March 1, 2007, meeting do not document the IRB's approval with changes of the advertisement for the above study. Such information is required to be included in the minutes under the regulations. However, verbal statements from the IRB Chair during the inspection and a copy of the advertisement revised by the IRB Chair indicate that the advertisement was not approved as submitted.

We acknowledge your statements that you revised your standard operating procedures regarding minutes to include the meeting minute elements required by 21 CFR 56.115(a)(2), and that you hired an individual to specifically take IRB minutes.

This letter is not intended to be an all-inclusive list of deficiencies for the above referenced study reviewed by the full IRB and through expedited review. It is your responsibility to assure that Coast IRB's practices and procedures fully comply with all applicable statutes and regulations.

Under 21 CFR 56.110(d), FDA, in order to protect the rights or welfare of subjects, is suspending Coast IRB's use of expedited review procedures until further notice because of Coast IRB's failure to follow FDA regulations regarding the use of expedited review procedures. FDA will remove this suspension after receipt of a satisfactory response that addresses the IRB's inappropriate use of expedited review and that provides details concerning the corrective action taken.

Page 4-Coast IRB

Because of the departures from FDA regulations discussed above, please inform this office, in writing, within fifteen (15) working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action without further notice.

If you have any questions, please contact Dr. Constance Lewin at [REDACTED] [REDACTED]. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1, Bldg. 51, Room 5354
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Sincerely yours,


Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

cc:
[] IRB Chair] M.Ed.
Coast Institutional Review Board
5475 Mark Dabbling Blvd., Suite 351
Colorado Springs, CO 80918



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Coast IRB's Free Test Drive offer applies towards initial protocol, informed consent form, and investigators drug brochure reviews only. \$1,300 value. Coast IRB, LLC pledges to protect the full confidentiality of all research studies sent to us for review. In 2005, the FDA removed the guidance prohibiting IRB shopping. As such, you are free to use our Free Test Drive offer to compare Coast's services with another IRB's concurrently. If, after comparing our services to those of another IRB, you choose not to continue with Coast IRB, we will destroy all the documentation we have on file associated with your study. Neither your money, research timeline, nor confidentiality will ever be at risk.