

**A DELICATE BALANCE: FDA AND THE REFORM
OF THE MEDICAL DEVICE APPROVAL PROCESS**

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WEDNESDAY, APRIL 13, 2011

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The Committee met, pursuant to notice, at 2:03 p.m., in Room SD-562, Dirksen Senate Office Building, Hon. Herb Kohl, Chairman of the Committee, presiding.

Present: Senators Kohl [presiding], Wyden, Nelson, Udall, Bennet, Blumenthal, Corker, and Ayotte.

OPENING STATEMENT OF SENATOR HERB KOHL, CHAIRMAN

The CHAIRMAN. Good afternoon. We would like to thank the members as well as our witnesses for being here with us today.

We are examining a very important topic today—the Food and Drug Administration’s management and oversight of the thousands of medical devices countless Americans rely on every day. The overall success of this process has become even more urgent for seniors in recent years.

Innovative technology has provided valuable lifesaving medical devices that have prolonged life and reduced suffering. We need to do all we can to make sure that these new medical products are getting to the market quickly as well as safely.

However, the FDA must constantly strive to maintain a delicate balance between safety and innovation. As we will hear today, this is an extremely difficult assignment.

The medical device industry has understandable concerns that significant changes in the medical device approval process contemplated by FDA could slow the rapid progress of new medical technologies to hospitals, patients, as well as the marketplace. They have also expressed concerns to the agency about a lack of consistent and clear guidance on how to get medical devices approved.

However, the drive toward getting new technologies to market should not be done at the risk of patient safety. Faulty medical devices, especially those implanted in the body, can have a disastrous impact on the health of those who use them.

Today, we will hear a firsthand account of the trauma that occurs when an implantable medical device must be removed due to a recall and device failure. As we hear about the cost to patients,

we should not forget the cost of recalls to the healthcare system as a whole.

We will have an update from the GAO, which has been investigating FDA's handling of the medical device approval process for the last several years. Somewhat disturbingly, this process has remained on the GAO's high-risk list of Government programs for 2 years now. GAO will also report on FDA's fast-track approval process for medical devices, which accounts for more than 95 percent of all medical device approvals and helps get medium- and low-risk devices to patients faster.

Finally, a top FDA medical device expert will discuss the complex and daunting challenges of overseeing medical device products in a time of tight budgets and exploding global medical technologies.

I believe we can find ways to improve safety in medical devices without hampering medical innovation. We look forward to hearing the ideas of our witnesses on how we can improve postmarket surveillance, improve adverse events reporting, and ensure that high-risk medical devices get the safety review that they need.

We look forward to hearing everyone's testimony today, and we turn now to Senator Bob Corker.

STATEMENT OF SENATOR BOB CORKER

Senator CORKER. Thank you, Mr. Chairman.

And thank all of you for being here, and I appreciate the breadth of panelists that we have and look forward to your testimony.

I think our goal is to achieve a balance. There are concerns on one hand that there may be devices that end up making it to the market where there are problems. And then, on the other hand, there are a lot of concerns where, for instance, in the European Union, a lot of times complex medical devices end up making it to the market 4 years earlier and actually create ways for people to have better ways of life.

There is concern about the safety, but there is also a concern that the FDA has become a place that is really about risk avoidance. I look forward to hopefully very balanced testimony today and hope at the end of this we are able to have a very good understanding of the direction the FDA ought to take.

I thank the chairman for having this. Obviously, this is very important to every American. Almost every American has some type of medical device that they use. So I thank you for this hearing today, Mr. Chairman, and look forward to the testimony.

The CHAIRMAN. Thank you, Senator Corker.
Senator Udall.

STATEMENT OF SENATOR MARK UDALL

Senator UDALL. Thank you, Mr. Chairman.

I want to thank you and Ranking Member Corker for holding this hearing today, and I want to thank the witnesses for taking time out of your busy schedules to share your various testimony with us.

I want to add to what the chairman said, which is we are here today to talk literally about life-altering and, in many cases, life or death issues for Coloradoans and for patients across the country. Our goal has to be to explore the steps necessary to make sure that

innovative and evolving technology represented by medical devices is as lifesaving and life-improving as possible.

Ms. Korgaokar, I know that the chairman will give you a formal introduction later. But as one of my constituents, Katie, I think you are from Denver?

Ms. KORGAOKAR. Yes.

Senator UDALL. I want to thank you for having the bravery to be here today and for sharing your story. Experiences like yours are why this hearing is so, so important.

The twin goals of the FDA require a very difficult, yet absolutely critical balancing act. Making sure, on the one hand, that doctors and patients have access to safe and effective devices while also fostering innovation in the medical device industry.

Dr. Maisel, I think in your written testimony, you assert that the FDA cannot ensure this balance alone, and I agree. The medical device industry must be a responsible and responsive partner in this effort. And additionally, those here behind the dais and the rest of Congress must vigorously exercise oversight role, as Chairman Kohl has brought us here to do today.

I regret that I have some prior commitments that will not allow me to stay and listen to everybody's testimony. But I have reviewed your written testimony, and I look forward to hearing the transcript from what I hope and, actually, I know will be a spirited and fruitful conversation during this hearing.

I don't think anyone expects that the approval, postmarket surveillance, and recall process for medical devices will ever be completely mistake free. However, the status quo needs work. And while I applaud the FDA for taking significant steps to tighten up this process with a goal of increasing safety and efficiency, I look forward to continued and expeditious action on the part of both the agency and industry to improve this process. We owe it to patients like Katie.

Thank you, Mr. Chairman.

Thank you, Senator Corker.

The CHAIRMAN. Thank you very much, Senator Udall.

Senator Ayotte.

STATEMENT OF SENATOR KELLY AYOTTE

Senator AYOTTE. Thank you very much, Chairman Kohl and Senator Corker, Senator Udall as well.

And I want to thank all of our witnesses who are here today, and I look forward to hearing your testimony.

I want to echo the comments that have already been made by the Senators on this panel. The FDA performs a very critical role. It is a critical regulatory agency that has to have a system that is safe, efficient, consistent, and thorough.

One of the issues that I am looking forward to addressing today is making sure that we have safe products that come forward through the process. I am deeply troubled by reports that our nation's leadership in medical technology could be declining as medical device technology companies, due to the review process, are increasingly looking to other countries for approval on innovative products.

We want to be on the cutting edge of making sure that we get the best technology that is not only safe, but the lifesaving products to United States consumers in as fast as possible process while making sure that it is safe. Medical device companies are a strong and vibrant part of the United States economy, and in my own home State of New Hampshire, we have over 50 medical device companies.

Over the last recess, I had the opportunity to visit three medical device companies that are doing very important work in our State, including one—Salient Surgical in Portsmouth—that is making technology that reduces blood loss during major surgery. And one of the things I was very struck by is that, when you walk into their conference room, you see the pictures on the walls of patients whose lives that they have saved.

Additionally, I visited another medical device company in New Hampshire, one called Next Step Orthotics that produces custom prosthetics for those who have lost a limb. Many of our wounded warriors, young people, old people, and even infants, are now being able to have that mobility and use, even though they have suffered situations where they have lost a limb. The technology is amazing. My point is that we want to make sure that we are on the cutting edge in this country. While protecting people like Katie, we must also make sure that this process doesn't put us behind other countries when looking at our global competitiveness.

I was deeply troubled to learn that we could be a couple of years behind other countries in regards to approving on safe technologies that are coming forward. So I look forward to hearing about the review process today and how we can work with you to make that process better, more efficient, and safer for patients.

Finally, I want to touch briefly on a topic that I know won't be the full subject of this hearing, but it is one that I am very concerned about and that I heard concern about from the medical device companies in my State. In the healthcare bill that was passed, there is a new tax on medical device companies that is actually, in my view, a tax on innovation.

It is not only a tax on the profit of these companies, but actually taxes their revenue. One of the concerns I have about that tax is that it is not going to allow the development of new research and development and technologies.

So I look forward to also working with my colleagues to address the onerous burden this tax places on an important part of our economy. The industry is not just important for the jobs that it creates in my State and across the country, but also for the important products that come forward to save and improve the quality of life of the citizens of our country, not only in New Hampshire.

So thank you all for being here today. I look forward to hearing your testimony.

The CHAIRMAN. Thank you, Senator Ayotte.

We will now turn to our panel of witnesses. First, we will be hearing from Katie Korgaokar of Denver, Colorado, who received a DePuy ASR hip implant when she was 36 years old, but after a few years needed revision surgery to remove the recalled device.

Next we will be hearing from Marcia Crosse, Ph.D., the director of the healthcare team in the U.S. Government Accountability Of-

ficie. Dr. Crosse will discuss a forthcoming GAO report on medical device recalls.

I would like to acknowledge my Judiciary Committee colleague Senator Grassley for allowing us to sign on to his GAO request on this issue and to discuss its findings here today.

Next we will be hearing from Diana Zuckerman, Ph.D. She is currently the president of the National Research Center for Women and Families. After a distinguished academic career, Dr. Zuckerman worked in the House of Representatives and served as a senior policy adviser to First Lady Hillary Rodham Clinton.

Next we will be hearing from Dr. Frederic Resnic, assistant professor of medicine at Harvard Medical School and director of a lab at Brigham and Women's Hospital in Boston.

Then we will be hearing from Ralph Hall, who is a distinguished professor at the University of Minnesota Law School, counsel to the Indianapolis law firm of Baker & Daniels, and a member of the board of directors of the Food and Drug Institute. Previously, Professor Hall was senior vice president and deputy general counsel at Guidant and headed Eli Lilly's environmental law group.

Next we will be hearing from Dr. David Nexon, who is a senior executive vice president of the Advanced Medical Technology Association, or AdvaMed, where he is responsible for the organization's domestic policy. Previously, Dr. Nexon served for more than 20 years as a Democratic health policy staff director for the Senate HELP Committee and its chair, Senator Edward M. Kennedy.

And last, we will be hearing from Dr. William H. Maisel, who is the deputy center director for science and chief scientist at the Center for Devices and Radiological Health at the FDA, where he works to guide the agency in science-based decision-making. Previously, Dr. Maisel served as associate professor at Harvard Medical School and founded and directed the Medical Device Safety Institute at Boston's Beth Israel Deaconess Medical Center.

Welcome to you. Welcome to you all.

And now we will start with you.

STATEMENT OF KATIE KORGAOKAR, PATIENT, DENVER, CO

Ms. KORGAOKAR. Chairman Kohl, Ranking Member Corker, and members of the committee, I thank you for giving me the opportunity to testify today.

I am here to give a patient's perspective of what happens when a defective medical device is released to the public. Specifically, I was one of the 96,000 unlucky people who received the DePuy ASR prosthetic hip that was recently recalled in August 2010.

The reason I needed a new hip was because I was born with a congenital condition known as Perthes disease. This disease caused the premature deterioration of bones in my hip joint.

Beginning in my early 30s, I began experiencing extreme pain on a fairly regular basis and had trouble with mobility. Eventually, the pain in my hip became so unbearable that I consulted with an orthopedic surgeon to see if there was anything he could do to relieve my symptoms. He recommended total hip replacement surgery.

Prior to my operation, my surgeon and I discussed the type of hip that he would use. He told me that it was a new, state-of-the art,

metal-on-metal hip that was specifically designed for young active people such as myself. He told me that the metal-on-metal design was superior to other designs and that it should last at least 20 years or more. The new state-of-the-art hip that the surgeon used was the DePuy ASR.

The initial hip replacement surgery was a huge success. Within 3 months of the surgery, I was essentially pain free and was able to engage in activities that had previously been off limits. The surgery truly changed my life.

Three years later, I met my husband, and we were married. Both my husband and I had always wanted to have children and immediately began trying to start a family.

However, about 8 months later, our plans changed. At this time, I received a letter from my surgeon advising me that the hip he had put in my body 4 years prior had been recalled. He told me that I needed to come in for an appointment so that he could do an examination.

When I heard this news, I really didn't understand the implications of what I was being told. In my mind, recalls were for dishwashers and cars, not body parts.

When I met with my surgeon, he explained that there was some type of design problem with the DePuy ASR that was causing excessive wear and tear on the metal components of the hip. As a result, the hip could be releasing metal debris into my body. My doctor told me I needed to have a blood test performed to see if this was happening.

There are two metals that I was told that were used that they were testing, which was cobalt and chromium. If the level of these metals were elevated, that meant there was excessive wear and tear occurring.

A few weeks later, my doctor called to tell me that the blood tests showed that I did have elevated levels. In fact, my levels were about 1,000 percent higher than they should be. At that time, I became very concerned. I had no idea how these metals would affect my body, and more importantly, I didn't know if they would impact my ability to have children.

After speaking with my doctor about these concerns, I learned that research had shown that excessive levels of cobalt in the blood could potentially impact the development of a fetus. I also learned that excessive levels of cobalt and chromium had been linked to several serious health conditions, such as cancer and cardiomyopathy. As a result, my doctor recommended that I have the hip replaced as soon as possible.

In January 2011, at age 41, I underwent my second hip replacement surgery. This time, the surgeon installed a more traditional hip with a polyethylene liner in the cup. The recovery from this second operation has been substantially more difficult than my first. The pain is much worse, and it has been extremely difficult to get around.

Only recently has my mobility improved to the point where I no longer need crutches. For the past 3 months, I have essentially been confined to my home, trying to recover.

Going forward, I have serious concerns about how this will affect my life. I am told that undergoing a hip revision surgery so soon

after the first will likely result in me experiencing more pain, dislocations, and other problems down the road. This is because each operation affects the muscles, tendons, and bones in the hip and makes it less stable.

I am also told that as a result of this, I may have to undergo one or more additional hip operations later in my life that could have possibly been avoided. Most importantly, however, I fear that given the small window I had to start a family, this operation may have forever prevented me from ever having children.

As I learned more about the ASR and the process by which it was approved by the FDA, I was shocked. Prior to this, I thought that any medical device that was actually being put into people's bodies had been extensively tested before it was released to the public. I had no idea that devices could be fast-tracked by the FDA with little or no testing.

I also assumed that the FDA had systems in place to monitor drugs and medical devices for potential defects so that prompt action could be taken if problems arose. Apparently, this did not happen with the DePuy ASR.

Additionally, I am concerned that the doctors who are actually installing these medical devices may not be fully committed to the well-being of their patients. Specifically, I recently learned that the surgeon who recommended that I have the DePuy ASR installed had actually received more than \$600,000 from DePuy in consulting income. A disclosure statement from DePuy is attached.

This was never disclosed to me before my surgery. Although I would like to think these payments had no influence on my doctor's decision to use the ASR, I will always have doubts.

Thank you, Chairman Kohl and Ranking Member Corker, for holding this hearing and giving me the opportunity to tell my story. I truly hope that you and your colleagues take a serious look at how medical devices are approved in this country and take whatever steps are necessary to make sure incidents like this do not happen again.

[The prepared statement of Katie Korgaokar appears in the Appendix on page 40.]

The CHAIRMAN. Thank you very much, Katie.
Marcia Crosse.

**STATEMENT OF MARCIA CROSSE, DIRECTOR, HEALTH CARE,
GOVERNMENT ACCOUNTABILITY OFFICE, WASHINGTON, DC**

Dr. CROSSE. Chairman Kohl, Ranking Member Corker, and members of the committee, I am pleased to be here today as you examine issues related to the regulation of medical devices.

Americans depend on FDA to provide assurance that medical devices sold in the United States are safe and effective. Today, I will discuss GAO's findings from our recent work examining FDA's pre-market review of device applications and ongoing work looking at the agency's oversight of recalls when medical devices are found to be defective.

Let me first provide some general background about medical device reviews. While FDA is responsible for overseeing all medical devices, about two-thirds of medical devices are exempt from FDA

premarket review. These are mostly low-risk devices, such as bandages and tongue depressors.

The remaining one-third of devices require greater regulation and must be reviewed by FDA before they are marketed. Over 90 percent of these devices are reviewed through FDA's premarket notification process known as the 510(k) process. The remaining small percentage of medical devices are considered high risk, including implantable or life-sustaining devices like pacemakers and replacement heart valves, and these devices are generally subject to FDA's premarket approval, or PMA, process.

The 510(k) process is less stringent than the PMA process. For 510(k) submissions, clinical data are generally not required, and clearance decisions will normally be based on comparative device descriptions, including performance data. For the more stringent PMA process, manufacturers typically submit clinical data, but FDA doesn't always require clinical data, even for implantable devices.

In January 2009, we reported on a key area of concern regarding FDA's premarket reviews. When Congress established FDA's premarket review system for medical devices in 1976, it envisioned that all high-risk devices would be subject to the more stringent PMA process.

Nonetheless, we found that more than 30 years after Congress acted, FDA had still not completed the regulatory steps necessary to require PMA reviews for some two dozen types of high-risk devices, including certain implantable devices. We recommended that FDA move expeditiously to address this issue.

Since then, FDA has issued a final rule regarding the classification of only one of these device types and has started, but not completed actions on the remaining 26 types of high-risk devices that can still enter the U.S. market through the less stringent 510(k) process. These include devices such as implantable hip joints of the type we just heard about. Since our report in January 2009, FDA has cleared at least 67 submissions that fall within these 26 types of devices that await final rules from FDA.

In addition to the concerns we identified with premarket reviews, FDA also faces challenges in postmarket surveillance of medical devices. In our ongoing review of medical device recalls, which we are conducting at the request of Senator Grassley and you, Mr. Chairman, we have identified gaps in FDA's processes that could allow unsafe or ineffective devices to continue to be used despite being recalled by the manufacturer.

Our preliminary analysis of medical device recalls found that firms initiated about 700 recalls per year. However, we found that firms frequently were unable to correct or remove all recalled devices, even those subject to the highest risk, or Class I recalls.

In addition, our preliminary findings indicate that FDA lacks clear guidance for overseeing recalls, resulting in inconsistencies in FDA's assessments of whether individual recalls were implemented effectively. We also found that FDA's decisions in reviewing recalls were often slow.

Finally, our ongoing work suggests that FDA is missing an opportunity to proactively identify and address the risks presented by unsafe devices. FDA does not routinely perform analyses of recall

data and does not use such information to effectively monitor and manage its recall program.

As a result, FDA could not provide basic information to explain trends, such as why the majority of recalls are medium risk, why high-risk recalls more than doubled between 2008 and 2009, or why many recalls have been ongoing for 5 years. We believe it is essential that FDA take steps to provide a reasonable assurance that medical devices entering the market are safe and effective and that the agency's postmarket safety efforts are both vigorous and timely.

Mr. Chairman, Ranking Member Corker, this concludes my prepared remarks. I would be happy to answer any questions that you or members of the committee may have.

[The prepared statement of Marcia Crosse appears in the Appendix on page 43.]

The CHAIRMAN. Thank you very much, Marcia.

Now we hear from Diana Zuckerman.

STATEMENT OF DIANA ZUCKERMAN, PRESIDENT, NATIONAL RESEARCH CENTER FOR WOMEN AND FAMILIES, CANCER PREVENTION AND TREATMENT FUND, WASHINGTON, DC

Dr. ZUCKERMAN. Thank you for the privilege of testifying at this important hearing.

I am president of the National Research Center for Women and Families, a think tank dedicated to improving the health of adults and children, and I am also testifying on behalf of our Cancer Prevention and Treatment Fund.

I was trained in epidemiology at Yale Med School, was on the faculty at Vassar and Yale, and a researcher at Harvard. I am currently a fellow at the University of Pennsylvania Center for Bioethics, and my FDA expertise started when I was a committee staffer in Congress.

Today, I will talk about our recently published study in the prestigious Archives of Internal Medicine. We studied the recalls from 2005 to 2009 that FDA designated as the highest-risk recalls because they could cause death or permanent harm to patients.

We found that most of those devices were not approved through the PMA process. They were cleared through the 510(k) process or, in some cases, even exempt from review because they were thought to be such low risk.

GAO has explained that FDA is ignoring the law when it clears high-risk devices through the 510(k) process. I will explain how that harms patients.

There are three essential safeguards that the PMA process has that are missing from the 510(k) process. Number one: clinical trials. There are no clinical trials required, so it is not tested on patients. Number two: no required inspections before they can be sold, so you don't know if they are manufactured as they are supposed to be. And number three: when they are cleared for the market, the FDA can't require postmarket clinical trials or epidemiological studies as a condition of approval.

So the FDA doesn't have the studies before they are allowed to be sold, and they can't require them as a condition of approval to make sure they are safe after they are sold.

Defenders of the status quo have said that what is important is that less than 1 percent of device applications are later subject to a high-risk recall, and that might make sense from a business point of view, but it really doesn't make sense from a public health or public policy point of view. Americans are dying and being harmed because their devices are not being tested before they are sold and, in some cases, put in their bodies.

As a scientist and a logical person, I believe that, if a device can kill you, it is not a low-risk or moderate-risk device. And I am not talking about lightning striking out of the blue. I am talking about an implant that deteriorates in the human body or a diagnostic test that is not accurate. Those are predictable but life-threatening problems that have caused recalls, and we can reduce those.

We don't celebrate every time we eat a meal that doesn't poison us, and yet Congress has recently improved the food safety system. And I just want to say it is wonderful that Congress has done that, even though food is quite safe, and similarly, we could save a lot of lives not just in food safety, but also in device safety.

Devices are common. Those of us who wear contact lenses or hearing aids, or have a replacement hip or knee, or had Lasik or Botox, or use test strips for diabetes, we rely on medical devices every day.

More than 430 million devices were subject to high-risk recalls in just the first 6 months of last year. That is more than one device for every man, woman, and child in the United States. It doesn't make sense that standards for even the most innocuous drug, such as a constipation medication, are more rigorous than for lifesaving medical devices.

Analyses that have been done that are similar to our study, such as Mr. Hall's and AdvaMed's analysis, would not meet the standards of a peer-reviewed medical journal or even of the research methods course that I used to teach. I won't go into statistical details, but I am happy to answer any questions about that.

There were almost 8,000 moderate-risk recalls in the last 5 years, such as Katie's hip. If you add those to the 113 high-risk recalls and divide even by Mr. Hall's estimated 20,000 submissions of devices, devices would not have a 99 percent safety record. It would be 60 percent. And if you use the numbers that GAO has provided, which was 700 recalls per year, then still the safety record would be about 82 percent. So that is much, much lower than the 99.5 percent that has been quoted and that you will be hearing about from other witnesses.

We need to count moderate-risk recalls, not just high-risk recalls because, as you have heard from Katie, they are hugely expensive and debilitating, and there is also the risk of death from additional surgery.

We don't know how many people die every year from unsafe medical devices because hospitals are required to report them, but doctors are not.

Even so, there were almost 5,000 reported deaths from medical devices in 2009 and hundreds of thousands of serious complications, and these are considered the tip of the iceberg because doctors don't report them to the FDA.

In conclusion, lives could be saved and patients would spend less time in the hospital if FDA implemented the law as required, as GAO has specified, and billions of Medicare dollars could also be saved.

The 510(k) process may be acceptable for devices that are truly low or moderate risk, but not for implanted devices or those that diagnose or treat potentially deadly diseases.

Thank you for the opportunity to testify. And I know that some of these numbers are rather hard to deal with, and I would be happy to answer any questions about them.

[The prepared statement of Diana Zuckerman appears in the Appendix on page 65.]

The CHAIRMAN. Thank you so much, Diana.

Now we will hear from Frederic Resnic.

STATEMENT OF FREDERIC RESNIC, ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL AND DIRECTOR OF THE CARDIAC CATHETERIZATION LABORATORY, BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MA

Dr. RESNIC. Chairman Kohl, Ranking Member Corker, Senator Ayotte, I would like to thank you so much, and as well as your staff, for the privilege of testifying today.

I respectfully refer you to my submitted testimony for details regarding my research in the area of medical device safety monitoring and for further information regarding the issues that I will only discuss briefly today.

To start, I am an interventional cardiologist, practicing at Harvard Medical School, where I use innovative medical devices daily in the treatment of my patients. I have, therefore, witnessed the tremendous benefits that medical devices can provide, and I have also seen the devastating complications that can occur when they fail.

In addition, I lead a research program funded through the NIH and FDA, investigating strategies to monitor medical device safety through continuous surveillance techniques.

To begin, medical devices, regardless of the approval pathway, will rarely, but inevitably fail, causing injury and even death. Despite the best-designed clinical trials and diligent premarket review, we can never, never know exactly how devices might cause harm until enough real-world experience is gained.

Unfortunately, the systems currently used to assure that medical devices are safe after market approval are really a patchwork of voluntary and passive event-reporting mechanisms. These systems rely on individual case reports submitted to the FDA, which then seeks to determine whether emerging trends indicate real safety problems.

Despite efforts to encourage reporting, the GAO has estimated that less than 1 in 200 actual device failures are reported to the FDA, tremendously limiting the information available. While these passive systems can identify previously unexpected safety concerns, they do not provide any information regarding the real-world usage of the devices or what is called the denominator data. Therefore, we can't understand the actual rate of device failure and can't compare one device to another.

Despite the challenges of the current systems, as well as the unique challenges of medical devices as opposed to medications, I believe there is a clear path to improving medical device safety monitoring that would not stifle industry innovation. This strategy is based on using active and continuous surveillance of health registries to detect safety signals in a timely manner.

Computerized tools are capable of monitoring hundreds of high-risk medical devices simultaneously, able to constantly watch accumulating database of clinical experience. Much like a smoke alarm, such systems can trigger an alert when the rate of a device failure or a complication rises above a threshold that would provide the analysts at FDA or other stakeholders with additional tools to drill down to explore the possible causes of safety alerts.

Recent pilot studies performed by my research group and others have used these continuous surveillance techniques to detect safety risks for heart stents, as well as to identify device failures years before the current passive systems would have been able to do so. On the basis of these pilot studies, leading U.S. experts in healthcare safety and quality have called for broadly applying automated prospective surveillance of medical registries as a principal way to improve the medical device safety surveillance that is currently used in the United States.

Of course, the first step in moving to this model of continuous safety surveillance is to address the critical need and current deficiency for detailed medical device registries. While detailed registries are mandatory in many countries, there is no U.S. system to assure that registries exist for high-risk, even very high-risk implantable devices, and no resources are directed to support these efforts.

Despite this, several nonprofit professional medical organizations have recognized the critical need for such registries and have spearheaded their development in an effort to analyze and to improve the quality of healthcare. I would cite the American College of Cardiology, which has put together several of these registries containing over 3 million records from over 1,000 hospitals. Also the Society of Thoracic Surgery and new efforts from in orthopedics, ophthalmology, and surgical material implants are all in development.

Importantly, FDA, through the new MDEpiNet initiative of the Center for Devices and Radiological Health, has been instrumental in trying to bring these dataset owners together with safety scientists to collaborate on device safety surveillance pilot projects. Another innovative effort has been the INTERMACS registry. It is a public-private partnership that involved the NIH, CMS, FDA, industry, and academia, which collects information on every patient who underwent implantation of a very high-risk device, a mechanical heart pump.

As part of this registry, CMS actually requires participation in order to qualify for payment, and also the registry satisfies the FDA's postapproval condition of approval requirements, thus redirecting resources spent by industry toward a more sustainable and generally usable and valuable resource.

So, in summary, the postapproval monitoring of medical devices in the United States, I believe, requires significant enhancement to

avoid preventable injury and death to patients treated with high-risk medical devices that infrequently, but predictably, fail. I believe that, aligning incentives, the U.S. can establish a comprehensive medical device registry that will continuously monitor for safety signals, and I would respectfully ask the committee to consider the following recommendations.

First, FDA, in collaboration with CMS, should mandate detailed information regarding high-risk medical devices be universally submitted to national registries.

Number two, registries should be operated by independent academic or professional medical societies as part of public-private partnerships, informed and guided by MDEpiNet and the FDA's Sentinel program.

Third, the FDA should redirect the resources currently spent by the medical device industry on limited condition of approval studies to support medical device safety registries and surveillance.

Fourth, automated safety surveillance should be uniformly applied to these registries to continue monitoring each and every high-risk device for safety over time.

And the results of these surveillance efforts should be provided in near real time to the FDA to interpret and potentially relay to stakeholders, as well as to providers and patients, as well as to device manufacturers, to support in their innovation and refinements in their product design.

Thank you so much for the opportunity to present.

[The prepared statement of Frederic Resnic appears in the Appendix on page 72.]

The CHAIRMAN. Thank you very much, Mr. Resnic.

Now we will hear from Ralph Hall.

**STATEMENT OF RALPH HALL, DISTINGUISHED PROFESSOR,
UNIVERSITY OF MINNESOTA LAW SCHOOL, MINNEAPOLIS, MN**

Mr. HALL. Chairman Kohl, Ranking Member Corker, members of the committee, I appreciate the opportunity today to discuss with you the important issues of medical safety.

I am going to concentrate on three broad topics—medical device safety, postmarket authorities, and recall authorities. My emphasis is on systems and authorities, as compared to individual implementation in specific cases, and what I hope to do is to provide information about the authorities that the agency currently has.

But to start, let us talk about the safety issues. When the debate over the 510(k) program first began in earnest several years ago, I was struck by the fact that there was no good data assessing at a system level the performance of the 510(k) system. It was a collection of anecdotes and opinions on all sides.

That struck me, and so, therefore, with the financial support of the Kauffman Foundation, which was with complete academic freedom, I undertook a systemic study of the 510(k) and PMA systems from a safety perspective. We used Class I safety recalls as the starting point because those are the high-risk safety issues. Other studies use the same starting point. And it is important to note that FDA, not industry, is the one that assigns that classification.

We coded these for a significant number of factors. Most importantly, we coded these for the reason for the recall. And if you want

to improve the premarket system by using this type of data, you have to understand the reason for the recall. Otherwise, you don't know what you are trying to solve.

For example, if you have a manufacturing problem, a mistake in the manufacturing line, 7 years after the product was approved or cleared, that is a quality system issue. That is not a premarket issue.

We also tried to establish a denominator to get an overall system performance. All devices have risks. Congress has actually established the balance point between the twin goals of improving public health via the availability of innovative devices and the safety that is so important to all patients. And that is, according to the statute, a "reasonable assurance" of safety and effectiveness.

And so, my study attempted to determine whether that congressional standard had been met. My conclusion, based upon the data, is that the 510(k) system is meeting the congressional mandate, that it is overall performing very well. Greater than 99.5 percent of the submissions do not result in a Class I recall.

More importantly, when you look at postmarket issues, more than half of all problems are from postmarket issues. And when you take that into account, it is greater than 99.7.

We also did a subanalysis of the data a number of different ways looking at product types. What we found is that a significant majority of all recalls were caused by quality system issues, both premarket and postmarket, rather than a lack of clinical data.

We also identified two concentrations of problems in recalls—one in AEDs, the other in infusion pumps—and the agency has, since then, commenced two initiatives to address those two product types. In my estimation, this is the type of data that can be used to improve the safety situation.

Using this methodology, we did not find a significant difference in performance between the PMA and the 510(k) systems. There is a lot of other data analysis we can get into if the committee so desires.

Moving to postmarket, the question that I am addressing is the authority the agency has. Others can address implementation. And I think it is clear if you look at the statutory authority, the agency has substantial authority in the postmarket realm.

For example, they have the authority to mandate registries, whether a PMA product or a 510(k) product. They have the authority to mandate postmarket studies. They have the authority via Section 522 to have postmarket studies for certain types of products. So there are a number of authorities they have that are specific to products.

They also have a wide variety of regulatory and statutory powers that apply universally. These are MDR reporting, recall reporting, inspections. And by the way, the agency can go and inspect a medical device manufacturer whenever the agency so determines. There is no requirement that they do anything in advance. They just show up.

And so, the agency has substantial premarket and postmarket authority to implement whatever sort of postmarket obligations they believe. They have the authority, even in the 510(k) system,

to get clinical data. And in about 10 to 12 percent of all cases, they require that.

In terms of recalls, again, the agency has substantial statutory authority. There are obviously voluntary recalls, but they have mandatory recall powers. They can seize products. They can go public with any concerns that they have. They can ban products. They can withdraw products, et cetera.

So, in conclusion, based upon the data that we have assessed, the 510(k) system is meeting the congressional mandate from the safety perspective, and the agency has substantial statutory authority in both the premarket and the postmarket arena, as well as in recalls.

Thank you very much.

[The prepared statement of Ralph Hall appears in the Appendix on page 81.]

The CHAIRMAN. Thank you, Mr. Hall.
Mr. Nexon.

**STATEMENT OF DAVID NEXON, SENIOR EXECUTIVE VICE
PRESIDENT, ADVANCED MEDICAL TECHNOLOGY ASSOCIATION
(ADVAMED), WASHINGTON, DC**

Dr. NEXON. Thank you, Chairman Kohl and Ranking Member Corker and members of the committee, for the opportunity to testify on behalf of the Advanced Medical Technology Association.

We are proud that the U.S. medical device industry is an American success story. We employ more than 400,000 workers nationwide, including more than 14,000 in your home State of Wisconsin, Chairman Kohl. We are one of the few manufacturing industries with a favorable balance of trade. Our wages are well above average.

A strong and vibrant medical technology industry is important to American growth and competitiveness. Most of all, it is important to American patients, who benefit from the new treatments and cures that our industry creates every day.

The reason we are so interested in your hearing today is that we in our industry recognize that we can only succeed as an industry if FDA is a strong and successful agency. So we welcome your examination of these issues.

I would like to make four main points for the committee. First, FDA has a strong record of assuring that medical devices and diagnostics are safe and effective. Professor Hall described his study showing extremely low recall rates for 510(k) products, indicating that FDA and industry are generally successful in keeping unsafe products off the market.

Other recent studies showed similar results, including one by Dr. Maisel. Recall rates are also very low for PMA products. Now I know you have heard some contradictory statistics today, and I would be happy to get into responding to those in the discussion period.

Of course, every process can be improved. Nothing is perfect, and our companies and FDA share a commitment to safety. But I want to emphasize there is no indication, no data that shows systemic failures in the assurance of safety that the current premarket review systems provide.

Second, the 510(k) clearance process has been criticized as a fast-track process that does not provide for adequate review. The data from the studies I mentioned show that this criticism is misplaced. In fact, the process is quite rigorous, but the data requirements are key to the nature of the device being reviewed and allow an effective path for rapid product improvement and medical innovation.

I want to emphasize, and this is something not everyone realizes, that FDA can require any level of data that FDA thinks is appropriate for a 510(k) submission, and that can be up to and including clinical trials.

Third, the biggest problem for FDA right now is the failure to assure that patients can have timely and consistent access to new treatments and cures. Since 2005, review times for 510(k) products have increased by 45 percent. Review times for PMA products have increased a whopping 75 percent. Difficulty in getting approval to start a clinical trial, inconsistency in reviews, and slow approvals are drying up investments in promising new therapies, and they are driving clinical trials and first product introductions abroad.

The result has been extremely negative for American industry's ability to compete. More important, it has been devastating for American patients, who must now wait 2 to 4 years longer than European patients to get new treatments and cures.

At the same time, the good news is that the Administration, from the President on down—and certainly the FDA leadership—understands that there is a problem and is taking a number of positive steps to improve the situation. We are hopeful they will be able to turn this situation around, and it is critical from the industry's point of view and patient's point of view that improvements come quickly because the current situation really is not sustainable.

Finally, let me address the postmarket issues. As detailed in my written testimony, and as Mr. Hall mentioned, FDA has robust postmarket authorities, including mandatory recall authorities.

Turning to the issue of surveillance, Dr. Maisel's testimony describes the numerous efforts FDA has underway to improve the quality and timeliness of surveillance. The most promising, in our view, is the use of electronic medical records in conjunction with unique device identifiers.

This will enable FDA to get real-time data on performance of individual devices across a large number of users and settings and will be invaluable to both FDA and manufacturers in identifying problems and targeting improvements. I am talking about the kinds of studies that Dr. Resnic identified.

I do want to add, though, a word of caution with regard to attempts to rely on single-purpose registries as a major strategy for improving postmarket review. Registries offer very valuable data, not just on device performance, but other aspects of quality care. And AdvaMed is pleased that our member companies are partnering with the American Academy of Orthopedic Surgeons to create a hip and knee registry with close to universal coverage.

But creating and maintaining single-purpose registries is labor intensive, costly, and requires a major commitment and leadership by providers since they are the ones that have the data on the performance of devices. In general, we think a more practical approach for most devices are registries based on UDI and electronic records,

where data is collected as part of the normal course of doing business.

Mr. Chairman, AdvaMed and its member companies stand ready to work with you and with the FDA to improve all aspects of FDA's device review and postmarket surveillance programs. Patients are our first priority, and we understand that our industry can only be strong when it partners with a strong and effective FDA.

Thank you very much.

[The prepared statement of David Nexon appears in the Appendix on page 107.]

The CHAIRMAN. Thank you, Mr. Nexon.

Mr. Maisel.

STATEMENT OF WILLIAM MAISEL, DEPUTY CENTER DIRECTOR FOR SCIENCE AND THE CHIEF SCIENTIST, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. MAISEL. Mr. Chairman, Ranking Member Corker, and members of the committee, I am Dr. William Maisel, Deputy Center Director for Science and Chief Scientist at the FDA's Center for Devices and Radiological Health.

I appreciate the opportunity to be here today to talk about the actions we have taken and the actions we will be taking to enhance medical device safety and to meet our public health goals of assuring the safety and effectiveness of medical devices while fostering important innovations.

I joined FDA's device center last summer while it was in the midst of arguably the most comprehensive programmatic review in its 35-year history. As part of that review, the center took a hard look at how we conduct our business, how we utilize new scientific information and make decisions, and how we can improve the health of American patients.

We have responded by taking strategic steps to improve the predictability, consistency, efficiency, and transparency of our pre-market evaluation and postmarket surveillance of medical devices and to strengthen our scientific decision-making.

In January of this year, we announced 25 actions we would take in 2011 to strengthen the 510(k) process, including development of new guidance, enhancement of staff training, and clarification of when clinical data is required in support of device submissions. But these are not the only actions we are taking. We have been actively collecting and reviewing safety and effectiveness information for the 26 remaining Class III 510(k) device types identified in the January 2009 GAO report, and we have committed to completing this evaluation and either reclassify to Class II or issuing a call for PMAs, for all 26 device types by the end of 2012.

Throughout the process of soliciting appropriate public input and conducting a thorough evaluation of devices with decades of marketing history, we have continued to promote device improvements and take actions to enhance the public health.

For example, our analysis of recall and adverse event data identified cross-industry concerns affecting external defibrillators, one of the devices on this list. And we took action by spotlighting required design, manufacturing, and purchasing controls and by collabo-

rating with the University of Colorado to establish a multi-city external defibrillator registry.

We are also transforming the way we conduct postmarket surveillance. Medical devices present unique challenges for postmarket monitoring because of their diversity and rapid product evolution. In 2011, we will issue final rules to increase electronic adverse event reporting that will enhance our ability to perform data mining, use automated computer algorithms to more efficiently and effectively review adverse event reports, and establish the unique device identification system.

This latter system will have a profound and positive impact on the Nation's ability to monitor medical device performance, reduce medical errors, track devices, and facilitate recalls.

The agency has also taken action to strengthen and improve its recall process. We have improved internal tracking of device recalls and reduced long-overdue device reclassification decisions by over 50 percent in the past year. Our analyses of recall data have been used to target strategic use of our enforcement resources to identify poorly performing devices, manufacturers, or manufacturing facilities.

We have also created a tool that better integrates analysis of pre- and postmarket data, including recall information, to provide our medical device reviewers with easier access to comprehensive information that spans the device's total product lifecycle. A similar tool has been made available to the public on the FDA's Web site, consistent with the agency's transparency efforts.

Industry shares the responsibility for medical device safety and the success of our device review process. Data shows that some companies submit poor quality applications, ask to meet with us, and then ignore our feedback or conduct poor quality clinical studies.

For example, a sample of 510(k) submissions from 2010 showed that, among applications we were forced to place on hold, more than half lacked a basic adequate description of their device. In another sample of submissions that required multiple FDA requests for additional information from manufacturers, nearly 60 percent repeatedly failed to follow FDA published guidance or recognize published standards.

These shortcomings waste valuable limited FDA resources and lead to unnecessary delays in the device review process. Nonetheless, under the 510(k) program, the pathway used for 90 percent of the devices we examine each year, 90 percent of our reviews were completed in 90 days or less, and 98 percent of the reviews were completed in 150 days or less, as we committed to do under the Medical Device User Fee Act.

FDA evaluates thousands of medical devices annually, and the vast majority of these devices perform well and improve patient health. We are taking actions to further strengthen our scientific decision-making, our premarket evaluation, and our postmarket surveillance of medical devices.

The United States is the global leader in medical device development, and FDA's medical device center will continue to support this country's position as the leader in safety, medical device technology, and innovation, while we continue to make good on our

commitment to promoting and improving the health of the American public.

Mr. Chairman, this concludes my formal remarks, and I would be pleased to answer any questions of the committee.

[The prepared statement of William Maisel appears in the Appendix on page 120.]

The CHAIRMAN. Thank you very much, Dr. Maisel.

Before we begin our questioning, I would like to call on Senator Bennet for a statement.

STATEMENT OF SENATOR MICHAEL BENNET

Senator BENNET. Thank you, Mr. Chairman.

And I would like to thank you and the ranking member, Senator Corker, for holding this important hearing.

I did want to come by and recognize Katie for coming here and testifying, not just the inconvenience, but the courage to come and testify on behalf of so many people across the State and across the country that have suffered through some of these issues.

It is a balance that we need to figure out a way to strike in our State, and my statement speaks to that. But your voice is very important to this conversation. So thank you for being here today.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Senator Bennet.

Katie, again, we will start with you. In light of your difficulties, we would like to know what advice you have to give to people who are facing their first procedure.

Ms. KORGAOKAR. Honestly, right now, it scares me because I thought I was making the right decision with the doctor I chose. But I don't know what advice to give.

The CHAIRMAN. If you were starting over, what kind of precautions might you have taken?

Ms. KORGAOKAR. I don't know that there is any I could. I mean, I researched the doctor. I picked him because of his standing, and the device he put in, I just had faith in it. I don't know what I, as a patient, could have done to prevent this.

The CHAIRMAN. What advice would you give us? As we have this hearing and we are trying to install some procedures, some ideas, some thoughts, what advice would you give us?

Ms. KORGAOKAR. Well, I definitely think that there needs to be a balance. But it still blows me away that something that goes into somebody's body can get approved without proper testing. And frankly, at least for the hips, there were hips that were in place that proved themselves to be good. But this state-of-the-art one that he put inside me, I don't understand why it couldn't have been tested properly and then come out when they knew it was good to go.

The CHAIRMAN. So you are saying we need to do a lot more testing, moving forward?

Ms. KORGAOKAR. Yes.

The CHAIRMAN. To be certain that what goes inside someone's body is absolutely safe?

Ms. KORGAOKAR. I absolutely agree with that, especially having to go through a second surgery.

The CHAIRMAN. Okay. Marcia Crosse, you noted that one major problem in conducting recalls was finding the devices. In conversations with committee staff, Johnson & Johnson discussed the difficulty of locating all of the recalled hips that were implanted in patients. Some are hard to track down.

How is it that innovative device firms cannot locate some customers or users? Would FDA's proposed unique device identifier or some similar mechanism help fix this problem?

Dr. CROSSE. Well, we are looking at the unique device identifier initiative that was required under the FDA Amendments Act, and we will be reporting on that in our forthcoming report on device recalls. It certainly could help, but it is not something that is going to be simply accomplished or quickly accomplished because it is very complicated.

You think about all the bar codes that exist on products in your grocery store or your drug store, and that is the same concept here. But you can't really have a bar code that is going to be in somebody's body. So you have to have some other mechanism for tracking that device and getting it into the proper records, and certainly registries are one approach that could be used.

But you also have to think about whether or not every physician's office, every hospital is going to have the equipment, the systems in place to be able to use any kind of a consistent approach and the variety that you would have to have for things that come in boxes of a dozen, as opposed to an individual device that might be implanted in somebody's body.

So it is not simple, and it is not going to happen quickly. It can help.

The CHAIRMAN. Okay. Before we turn to Senator Corker, I will ask you, Diana, a question of a lot of conflicting data was presented here about the fast-track 510(k) process and whether it should be changed. You have studied the medical device approval system for a long time. In your opinion, what is the most critical medical device approval issue that FDA needs to address?

Dr. ZUCKERMAN. Oh, that is a tough one. I think that actually what Katie said cuts to the core of the issue, and I should say I also had the pleasure of having a hip replacement last year. So I can speak as a patient, too.

Here I have all this knowledge. I knew to look on PubMed and all the published medical journals. But there were no data on different hips and which ones would last longer and which ones are better. No data were available at all except some registry data from Scandinavia, and those were on particular models that aren't sold in this country.

So I really was stuck with no safety data. And the one thing you can do that Katie has done after her surgery is find out if your doctor has taken a lot of money from a company. And that can make you more suspicious, but it doesn't tell you whether the doctor is any good or not.

So, to me, the problem is it is not that all medical devices should go through a PMA process. I am not saying that. What I am saying is if you have an implanted medical device, doesn't it make sense to do a clinical trial first, to test it on a human being?

And when we look at the high number of recalls, if you look at moderate risk as well as high-risk recalls—we didn't look at the low-risk recalls—how many of them there are of 510(k) products, as well as PMA products. But you expect high-risk recalls for a PMA because those are high-risk devices. If 510(k) devices are supposed to be moderate and low risk, they shouldn't be killing people.

So if you hold devices to a higher standard of having clinical trials beforehand and inspections, whether the FDA has the authority to do it or not, they haven't done it. And the tradition has been not to do it. And if your law doesn't require it, if it says "may" instead of "shall," everybody in this room knows what that means.

So you have to have a standard that is high enough to protect patients. And yes, that will slow things down, but it would also have slowed down what happened to Katie. Had that hip been subject to clinical trials, most likely they could have done the blood tests and found out about the problem prior to putting it on the market. At the very least, if not prior, then more quickly after it went on the market.

So studies, clinical trials, either beforehand or as a condition of approval are the most critical issue. I don't think postmarket should take the place of premarket. I think you have to have the studies premarket for anything that is in the human body or life-sustaining or lifesaving, but then also have protections afterwards.

The CHAIRMAN. Thank you.

Senator Corker.

Senator CORKER. Thank you, Mr. Chairman.

Just to follow on with that line of thinking, Mr. Hall, if you look at the situation Katie just talked about and Dr. Zuckerman just discussed, should there be testing of that type? Or what was it, in the case of Katie, that caused this particular issue to be a problem?

Mr. HALL. Senator, I am not conversant with all the details of the ASR situation. So I can't comment specifically on that.

What I can say is that, from the data that I have seen, and I think it is consistent across the board, quality systems, QSRs, quality system regulation, is the key way to have the greatest positive impact on device safety as compared to other things. And in our data, 90 percent of all recalls were because of quality system.

And it is important to understand that quality systems are not just manufacturing. It is total product lifecycle. It begins with design, design input, design validation, bench testing, manufacturing, postmarket surveillance, et cetera. So, hopefully, quality system requirements would be the best way to identify these issues.

Senator CORKER. The two of you, I know that you all are on different ends of the spectrum. Your numbers are quite different. I mean, you are at 98 and 99.5. And you are at 60 or 80.

Since, obviously, I would say that Dr. Zuckerman is challenging your numbers, would you want to respond to that? I mean, it is a pretty vast difference. We are not talking about a percent or two.

Mr. HALL. Sure. Let me make a couple of comments. When you look at the differences in the study, there are several key differences.

First of all, we looked at the reason for the recall, and the study that Ms. Zuckerman referenced did not. We think that is critical because many recalls, the majority have nothing to do with the pre-

market system. And so, to use premarket, to analyze the premarket system using recalls that have nothing to do with the premarket system creates a results that has little validity.

Secondly, the study, our study used a denominator. Theirs did not. I think what you heard from the GAO is that the ratio of PMA to 510(k) devices is 1-to-10 or 1-to-9. The study, both of the studies—and interestingly, we start with the same dataset, around 112, 113. You have a 4-to-1 ratio approximately of 510(k) recalls, all cause, compared to PMA. That is not surprising, given the 9-to-1 ratio that we start with.

Next, we also do not consider that the recall classification should be linked to the approval classification. Those are two separate questions. For example, you can have a very low-risk device that because of the particular issue has a very high risk to it.

And finally, if you look at the study that they reference, it contains a number of incorrect, inaccurate statements about the 510(k) and the PMA status and the law. What our study attempted to do was to look at the relevant data, recalls for premarket reasons, looking at Class I high safety issues, and with that then try to understand how the system is operating.

Dr. ZUCKERMAN. Yes, thank you—

Senator CORKER. Is there any validity in the argument he just put forth?

Dr. ZUCKERMAN. Sure. I would like to correct a couple of things he said. I used your denominator Mr. Hall. Using your same denominator of 20,000 and using the same numerator—sorry to get into this technical stuff—of recalls. You didn't look just at the recalls that were premarket due to design issues. You looked at all the recalls that were high-risk recalls.

The difference in the statistics, the huge difference between 99 percent and 60 percent or 80 percent has to do with whether you count the moderate-risk recalls. You looked only at high-risk recalls and you say that any device that was submitted to the FDA—not even approved, but submitted—is your denominator, and your numerator is only the high-risk ones. If you are assuming that if it wasn't a high-risk recall, it is safe, then you get 99 percent.

But if you consider that a moderate-risk recall also means a product is not safe because, as in the case of Katie's hip, that is a moderate-risk recall. There were over 170 knees and hips and joint components recalls, involving hundreds of thousands of devices in the last 5 years that are all moderate-risk recalls, but all require additional surgery or rehab, or have other problems. If you count those moderate risk recalls, then it goes down to 60 percent if you use the numbers we used for recalls, or to 82 percent if you use GAO's numbers.

We respect GAO's numbers. Ours differ because we looked at specific models, model numbers, and the GAO combined model numbers of the same device. So there are different legitimate ways to look at it. I am saying that I don't think that a device is safe just because it is not subject to a high-risk recall. A moderate-risk recall can cost \$35,000 and a lot of pain to fix.

Senator CORKER. Dr. Maisel, and it is interesting, it seems that you have a patient here on the panel. You have a sort of more trial bar orientation on the panel. You have sort of the device orienta-

tion on the panel. And nobody is particularly happy with the FDA. And I don't know whether you consider that to be success—you know, a lot of times here if everybody is mad at you, you have kind of hit the sweet spot—or whether that is tremendous failure.

I wonder if you could discuss that because, candidly, I don't know of anybody that is particularly happy with the FDA. And I am wondering if you are seeking anything from us to change that or if you might respond to the fact that I don't think anybody on this panel is really thrilled with you guys.

Dr. MAISEL. Well, Senator, thank you, first of all, for the opportunity to be here today and to comment.

And I would like to personally thank Ms. Korgaokar for taking the time to be here and for her compelling story.

I personally have practiced medicine for 19 years and sat in rooms with patients who, unfortunately, had recalled medical cardiac devices that also sometimes require surgery to remove. So I am very familiar with what patients experience and the challenges that physicians experience when trying to help their patients.

We conducted a very thorough programmatic review over the last 18 months, and we have identified areas that we think need improvement. We would like to deliver more consistency and transparency in our decision-making. We would like to strengthen our science-based decision-making, and we have outlined a number of actions that we have already started taking to strengthen the program.

I think one critical factor here is that we believe that smart and focused changes are appropriate. For example, one area is focusing on the Class III 510(k) devices that have already been identified by the GAO and that we are actively working on and have committed to either reclassifying or calling for PMAs.

In Dr. Zuckerman's study, 13 of the 80 recalls that she highlights are in that group. So we certainly recognize that there are some focused areas we need to evaluate and strengthen.

I am not going to get into the war of numbers to my right over here, other than to say as part of the IOM committee evaluation that is underway, there was detailed FDA data presented that was based on all of the recalls, not just one class or another, and showed a 510(k) recall rate of approximately 1 to 1.5 percent per year.

So, from an agency standpoint, I think we find that the most reliable data. And that is publicly available, or we would be happy to provide that analysis for you.

I do think that a number of the challenges we face in postmarket monitoring have been outlined here, and there are some unique issues with devices that are different than drugs that are worth mentioning. Number one, it is sometimes very difficult to even know whether an adverse event is due to the device or due to the surgical procedure that was used to implant the device.

Now in the case of the hips, that wasn't the issue. But sometimes, based on some of the data we get, it is not so clear whether the device is malfunctioning or whether it is a complication of a medical procedure. Oftentimes, the adverse event reports we get are cryptic and don't contain enough information. Sometimes we

don't even know what device or what model of device has caused the problem.

And so, we think that the changes we are implementing with electronic medical device reporting of adverse events and with the unique device identifier system will really revolutionize the way that we can perform postmarket surveillance.

With regard to hips in particular, we have also undertaken efforts to form an international consortium of orthopedic registries. And in fact, in the Federal Register today is the notice for a meeting that is occurring next month where representatives of more than a dozen orthopedic registries from around the world, including from the UK, Australia, and other countries, come together so that we can make a better system for monitoring these important products. And other efforts will be underway as well.

Senator CORKER. I know we have other folks that have questions. I have a number of other questions. I thank all of you for your testimony.

The CHAIRMAN. Thanks, Senator Corker.

Senator Blumenthal.

Senator BLUMENTHAL. Thank you very much, Mr. Chairman.

I want to thank Senator Kohl for having this hearing today on this critically important topic and Senator Corker for your leadership as well.

You know, let me just state very bluntly, my time is limited, and I want to ask some additional questions as well. But my experience as a State law enforcer for 20 years leads me to conclude, particularly my interaction with patients like Katie Korgaokar—and thank you for your courage in being here today—that this system simply isn't working. It is inadequate. It is broken, needs to be fixed. And I thank Dr. Maisel for your recognition, the agency's recognition that the system right now is not performing acceptably to protect people from unacceptable levels of risk and injury.

I am reminded of the statement that a minor procedure in surgery is something done to somebody else's body. And a minor risk of severe injury, when we are talking about these kinds of devices, is something that happens to somebody else.

So I think there are a range of areas that really need very close scrutiny and action. I mean action now, immediately—not postponed to the future—that have to do with the need for clinical trials more often, more thoroughly. Instead of the expedited 510(k) procedures when it is currently used, the need for more robust postmarket surveillance and quicker action so that the doctor who may have believed in good faith that Katie's device worked and would not cause the kinds of metals released into her system that happened can be warned about it more quickly and can be compelled—through proper incentives, liability, if necessary; heightened penalties—to stop using that kind of device.

And let me just ask Dr. Maisel whether the FDA is prepared to expedite the kinds of improvements that you have been discussing here today and what can be done to expedite them and whether there needs to be action from the Congress to expedite them?

Dr. MAISEL. Well, I thank the Senator for your question.

We have exerted a considerable amount of our resources and manpower over the last 18 months to evaluate the program be-

cause we recognize how important it is to the American public and their health. We are expediting a number of efforts. We outlined 25 actions we are taking in 2011 that will be completed in 2011. These aren't actions that we are talking about over the next 5 years or 10 years. These are things we are doing right now to improve device safety for the American public.

They include things like issuing guidance on what type of changes to devices require clinical data. They include things like training our staff and industry so that the quality of the submissions we get and the quality of the reviews can improve. We are taking actions in the postmarket surveillance setting as well.

So in answer to your question, I would say we are expediting a number of these changes. Now other changes admittedly take time, such as the implementation of the unique device identifier. We are issuing a final rule this year. We have been talking with industry and stakeholders about the implementation of that because it is a sea change in how we will conduct business.

And so, it will be implemented in phases, focusing first on the highest-risk devices. So, again, in answer to your question, we are expediting the changes to the program that are necessary.

Senator BLUMENTHAL. And what can we do to encourage those kind of changes so that there is a consistency and a steadfastness in implementing them and so that they are even accelerated?

Dr. MAISEL. Well, I think, in all seriousness, you took a very good step this week in passing a budget for FY 2011 or the continuing resolution.

Senator BLUMENTHAL. Do you need more staff? Is that the problem? You know, by the way, when I say the system isn't working, I am not talking about the people who work with you and for you, because the system is not of their making. But I am wondering whether more resources are the problem?

Dr. MAISEL. Well, the number of device submissions that we have to evaluate has increased, and the complexity of devices has increased. And we are a strained organization.

We certainly appreciate the funding, and we are in negotiations for reauthorization of the Medical Device User Fee Act that will be coming before Congress in Fiscal Year 2012, and through that process, we will certainly make clear what our needs are so that we can have the strongest possible organization.

Senator BLUMENTHAL. Thank you very much.

I thank everyone here for your testimony. My time has expired. I am hoping to stay for another round of questionings.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Mr. Blumenthal.

Senator Ayotte.

Senator AYOTTE. Thank you, Mr. Chairman.

Dr. Maisel, I just wanted to follow up. You had mentioned an Institute of Medicine study on the safety of the 510(k) process and looked at all classes of recalls. Before you joined the FDA, did you participate or assist in that study?

Dr. MAISEL. I was commissioned by the Institute of Medicine prior to my joining FDA to conduct a study on recalls for the 510(k) program.

Senator AYOTTE. So that Institute of Medicine study which you looked at that came up with an overall range of 1 to 1.5 percent in terms of the recall rate, is that one you have confidence in?

Dr. MAISEL. I have confidence in that study, yes.

Senator AYOTTE. First, I'd like to address questions both to Dr. Nexon and Dr. Maisel. There was a study that I am familiar with that was done called the Makower study which found that the United States is at risk of losing its global leadership position in medical technology innovation.

The study found that the unpredictability and inefficiencies of the U.S. regulatory process are making it difficult for companies to get life-changing medical products into the hands of clinicians and patients. On the other side, as Senator Blumenthal mentioned, there is the piece of ensuring safety, but also getting these products that can save lives in the hands of patients in an appropriately expedited fashion.

One of the issues I raised in my opening statement is that some studies that have, are saying that, on average, devices are available to United States citizens two full years later than patients in other countries.

So I guess I would direct my question to both of you, really to Dr. Nexon. What can we do to improve the regulatory processes and increase patient safety at the same time to be competitive with other countries? I would hate to have us be in a position where we cede our global leadership in this area or deny patients access to technology that could be lifesaving.

Dr. NEXON. Well, thank you very much for your question, Senator.

I think there are a couple of steps that need to be taken. FDA has identified a number of them themselves in their review of the 510(k) process and their new science reports. There needs to be better training of reviewers. The study revealed that large proportions of reviewers didn't have understanding of the basic regulatory terms.

There needs to be greater guidance and consistency for industry so that when industry submits a product for approval, it knows what the data standards are and then doesn't find out after the submission is in that they had to redo the trial because they didn't get clear guidance in advance of what FDA expected.

There needs to be better management at FDA just to enforce consistency of review and that their speed of review—the FDA recently did an analysis where they found out that one of the greatest sources of delays in PMA products, getting PMA products approved, was a situation where the reviewer would change in the middle of the review, particularly if the lead medical reviewer went on vacation. You know, that is a management issue to schedule vacations better or to see that there needs to be specific attention to cases where those things occur.

There is a huge problem in terms of the IDEs, the investigational device exemptions, which you need to get before you can ever begin a clinical trial that involves human subjects. And it takes an inordinate amount of time to get those approved. Sometimes it is a matter of years before you can even start the clinical trial, six

months or more to get a meeting with FDA to discuss the nature of the trial.

So I think that there are a number of steps that FDA needs to take to really make the process work better for companies and for the agency. I think this will help the agency as well if there is more consistency and better management of reviews.

I don't think that there are fundamental changes that need to be made in sort of the legal structure or the requirements for different types of devices. I think those are pretty well set out, and it is a matter of applying them consistently and using good judgment when a device comes in for review.

And where there are problem areas identified, and there have been. Dr. Maisel, I think, alluded to—or Professor Hall alluded to AEDs and infusion pumps. They found specific problems from their reporting system, and they instituted new, very clear requirements for those products.

Now whether the industry agreed with all those requirements or not, it is a case where the FDA saw a problem, took action, and they did it in a way so that industry knew what was expected of them for the future.

Senator AYOTTE. Dr. Maisel, I would appreciate your comment on this. The other follow-up would have for both of you is, in looking at the comparisons with European approval versus the United States, is there an issue in terms of discrepancy in safety that we should be looking at? Safety is obviously important to consider as well.

Dr. MAISEL. Yes. So the Makower study that you referred to surveyed a very small percentage of the medical device industry. They got about 200 respondents out of a device industry that includes more than 10,000 individual companies. So we have to understand that this is a very biased, small representative study.

There was another study put out by the California Health Institute that looked at the review times for the U.S. compared to the European community. And for the 510(k) program, which is 90 percent of the devices that are reviewed in the U.S., the U.S. was faster and the device got to market sooner for the low-risk devices. It was about the same for the medium-risk devices. And for the high-risk devices, the EU was faster than the U.S.

So we need to understand what the issues are and what the timing is, and it is I think not accurate to say that every device gets to the EU market more quickly. I think the hip example is a great example because there were actually two hips that were recalled by DePuy. Both were on the market in Europe. Only one of them was on the market in the U.S.

And so, the "delay" in getting products to market in the U.S. is not necessarily a bad thing for products that aren't performing well, if we are asking for more rigorous data to support their approval.

Senator AYOTTE. I just wanted to add, obviously, I haven't done a scientific study, but just in speaking to many companies, particularly startup companies, large and small, I've been getting similar feedback in terms of concerns about where they are going to locate their companies and where they are going to develop new products. And so, that is where I come from in asking those questions.

Dr. MAISEL. And I think it is a great point, and we have, earlier this year, announced our innovation initiative, which is a comprehensive program to try to promote device development and innovation in this country, by strengthening the research infrastructure within the United States, identifying clinical trial centers that are particularly expert in medical device development. And we certainly recognize the importance of that as well.

Senator AYOTTE. Dr. Nexon, you had a comment?

Dr. NEXON. Yes, if I could just add a couple of things. I mean, the Makower study has come in for a lot of criticism from FDA. It was really a pretty large sample of companies. Two hundred small companies is a lot of companies reporting on almost very similar experiences.

It is also only one of three studies that has looked at this issue. There was a study at PricewaterhouseCoopers that used a different sample, primarily a large company sample, that found that the U.S. ranked seventh out of nine countries in the speed of regulatory approval.

And then there was also the California Health Institute study, which was just mentioned, which did find a substantial lag for the more complex devices and more innovative devices which are really the ones that are greatest issue for competition. So I think there is a big problem.

It is also the case that there was a study by the Boston Consulting Group, which was the only systematic study I know of the relative safety of the two systems, and found that the recall, incidence of recalls was about the same in Europe and the United States. Didn't seem to be much difference.

Now we are certainly not advocating for a European system of review. As Jeff Shuren, the head of the center, said, there is no inherent reason why the U.S. system has to be slower than the European system. And what the California Health Institute study showed that I think it was six years ago, on average, it took a year longer to get a product to patients than Europe. Now it takes four years longer. We ought to be able to do better than that.

And I can tell you my own experience when I am telling you this is not systematic, but it is from talking to lots of companies and lots of particularly of venture capitalists who invest in small companies that the problems at FDA are a huge deterrent.

I had one venture capitalist tell me that he was a fellow who has got investments in seven or eight small device companies. He used to take a case where he had an engineer, a doctor, and an idea, and he would be able to put money so they could bring that idea to fruition into products that would benefit patients.

Now his investors, which are often big pension funds, won't allow him to invest in any company that hasn't already got an FDA approval because the uncertainties of the approval process are so great. And that is not a system we can sustain if we are going to maintain American leadership.

Senator AYOTTE. I would add to Senator Blumenthal's question to you, Dr. Maisel, obviously to ask the committee how you think that we can help by taking action and to improve the process. And I would follow up to ask you, Dr. Nexon, do you have any thoughts in terms of whether there is a legislative fix that is needed?

Dr. MAISEL. Well, again, as I stated earlier, I think we are an increasingly busy center with an increasing number of applications and increasing complexity of devices. We have certainly committed to strengthening our scientific evaluation of these products, and the continued support from Congress for our program, as you have done, is certainly welcome.

Senator AYOTTE. Do you have anything to add, Dr. Nexon?

Dr. NEXON. Yes, I think the fundamental legislative structure is pretty sound. So I don't think additional legislation is required. I do think, as Dr. Maisel has pointed out, you need to maintain at least stable funding for the FDA, even in this time of tight budgets, if they are to meet these challenges.

And I think that the key really is the kind of attention that this committee and other members of Congress show to the FDA is important really to give it a priority. We were very heartened by the President's op-ed on the importance of streamlining regulations, and I think he even mentioned in the State of the Union the device industry as one area where FDA needed to do well if the United States was to remain competitive.

And I think those kinds of comments and that kind of attention is very helpful for the industry, and I think it is helpful for FDA to show that their work is valued.

Senator AYOTTE. Thank you both, and thank you all for coming to testify today. Appreciate the insight that you have given this committee.

The CHAIRMAN. Thank you, Senator Ayotte.

Senator WYDEN.

Senator WYDEN. Thank you, Mr. Chairman.

And without making this a bouquet-tossing contest, let me just tell you how much I appreciate particularly your tenacity in being willing to stay at these issues, and this is an important hearing.

Dr. Nexon, let me start with you. The longer that I am involved in the issues of public policy and healthcare, the more convinced I am that transparency and getting good information out to the public is one of the most important steps we can take as public officials. In terms of creating choice and competition and holding costs down, it is one of the best steps we can take.

For example, recently Senator Grassley and I introduced legislation that would allow, after 30 years, the opening up of the Medicare database so as to get information to the public about various claims and patterns. And as you know, there have been some extraordinarily abusive practices, and we have worked with the Center for Public Integrity, and Wall Street Journal has done yeoman reporting on this.

I want to ask you about how it relates to another matter, and it was triggered in my mind by a letter that the Group Purchasing Association wrote recently. And essentially, what they are concerned about, their assertion is the drug manufacturers enter into relationships with—excuse me, device manufacturers enter into relationships with doctors. These relationships are protected through what amount to gag clauses, contractual confidentiality agreements, and this prevents hospitals, according to them, from disclosing the price they pay for a device.

And their assertion is that, when you have these gag clauses, you go right to the heart of what I am talking about. There is no price transparency, and people aren't going to be able to look at the cost of various medical devices. And third-party groups can't find out. Patients can't find out. It is a very vexing problem.

So my question to you is—and you can tell me what you think of the Group Purchasing Association—what would you think about the idea of opening up and releasing price data on purchasing agreements to the public? It is Government money. There is Government money involved here.

Senator Grassley makes the point, colleagues, that I think is really the ballgame. Senator Grassley says people know about its farm payments. They know about defense contracting payments. He says we have got to find out this claims information.

So tell me what you think about the idea of industry opening up and releasing price data on purchasing agreements.

Dr. NEXON. Well, we are generally in favor of transparency. We are strongly in favor of releasing quality data to the American people. We think the FDA should be more transparent. We supported Senator Kohl's Physician Payment Sunshine Act because we think that was good for the public and good for the industry.

I will say, however, we are strongly opposed to releasing pricing data, and let me tell you why. Because it has to—

Senator WYDEN. So your position, though, is everybody else ought to have their data released, but you all wouldn't—

Dr. NEXON. Well, no, the fact is—the sad fact is, Senator, that, when you are talking about commercial transactions between institutional buyers, there are often confidentiality clauses. It is not unique at all to the device industry.

Auto manufacturer sells a car to a dealer, you know, what the prices and the discounts he provides are not generally available to the public. And that is true with many large transactions.

It is important to remember that the Government in the Medicare program—it is not true in something like the VA—and the public do not buy medical devices directly. Medical devices are bought largely by hospitals, large institutional purchasers, and then, when a patient goes to the hospital, he pays a price for a procedure which includes in some sense the cost of that device. But it is not that he is buying the device directly or necessarily that the price he pays has anything to do with the price the hospital negotiates for that device.

As a patient, I want to know what I have to pay. I am not concerned with what the hospital pays for electricity or gasoline or some other component of the procedure.

Now the question is if we release that price data, would it have a positive effect for the public or not? And the fact is that the current arrangements, which involve negotiations between relatively sophisticated buyers and relatively sophisticated sellers, have created an extremely competitive industry.

There has been a study by Guy King, the former chief actuary of the Medicare program, of prices in the medical device industry. And what he found was that, over an 18-year period, our prices have gone up one-quarter as fast as the typical medical price in-

dexes, so one-quarter as fast as everything else in the healthcare sector.

And we have gone up half as fast even as the general CPI, which, as you know, has been quite low in recent years. So we have a pretty good record of keeping prices low through competition under this negotiation between informed buyers and informed sellers.

There have also been studies, a study that was done by Bob Hahn and another—Bob Hahn is a regulatory specialist. And there is concern that if the prices were released not only would it inhibit our ability to enter negotiations, but it might end up resulting in actually higher prices paid across the board because of antitrust issues.

Senator WYDEN. I can tell you certainly with the example you gave of automobile companies and manufacturers, you are talking about private sector money. Here, despite the kind of chain of purchasing you have described, there is a lot of Medicare money.

I have other questions I want to ask, but my sense is that the Group Purchasing Association at least warrants our looking at these confidentiality agreements. These are gag clauses, and they prevent hospitals from disclosing the price that they pay for a device. I think that is right at the heart of it, and I think it warrants some further attention.

One question for you if I might, Dr. Maisel. What is your sense about the FDA review process and making it more transparent as you go forward with striking the balance between safety and speedy approval?

Dr. MAISEL. Well, as you know, FDA is very interested in providing transparent information to the American public, and we have an ongoing transparency initiative. And that carries over to the Center for Devices, where we have posted a variety of documents and provided access to public data increasingly over the last years.

For example, as I alluded to earlier, there is now a public Web site where you can go and type in a device type and find out about all the recalls and adverse events that have been submitted for that type of device.

We are bound because we do deal with confidential commercial information. So there are some limitations on the type of information that we can provide to the public. But we are certainly interested in providing decisional information as much as possible and have done so.

Senator WYDEN. All right. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thanks, Senator Wyden.

Senator Bill Nelson.

Senator NELSON. Thank you, Mr. Chairman.

I want to ask you two gentlemen, Dr. Maisel and Dr. Nexon, if you would comment on the tension between safety and the need to innovate new technologies. This industry is real big in my State, and I would like to get your two perspectives.

Dr. Maisel.

Dr. MAISEL. We often talk about it being a tension, but it doesn't have to be a tension. A good device evaluation for an innovative

product promotes safety. There can be innovative devices that improve safety. So there is a tension in the sense that longer evaluation of devices that requires more data has the potential to slow down getting an innovative product to patients. And if that product would improve public health, then taking a longer time actually has a net negative impact on the public health.

So that is the tension. The tension is striking the right balance in our risk analysis so that we can get a product to market to help patients in the right time.

Senator NELSON. Dr. Nexon, you are sitting on the other side and—

Dr. NEXON. Well, I actually agree with Dr. Maisel. I think there is a balance to be struck. I think the balance in the law, which Professor Hall mentioned, a reasonable assurance of safety and effectiveness is a reasonable standard. Device manufacturers should be held to a high standard of safety.

They should be able, before a device goes on the market, to present the data that gives a reasonable assurance that their devices will be safe and effective. The problem is that sometimes that can be interpreted in a way that makes the bar so high that products that can save lives or improve health don't get to market because test after test is required.

But we have no disagreement with the general approach that FDA takes. What we want is consistency, rapidity, ability to get answers, and reasonable standards, and I think those are goals that FDA and the industry share. And in the public, too. The patients as well.

Senator NELSON. Do you think there are undue delays?

Dr. NEXON. Pardon me?

Senator NELSON. Do you think there are undue delays in the approval?

Dr. NEXON. Yes.

Senator NELSON. Amplify.

Dr. NEXON. Well, as I think before you came in, I mean, what we have seen is a very severe deterioration in FDA performance over the last five years, and performance was not super before that. The time it takes in terms of elapsed time, not time on the FDA clock. The time, a recent study by the California Health Institute showed that the time it takes to get a 510(k) product approved has increased 45 percent since 2007, and the time it gets to get a PMA product approved has increased a whopping 75 percent. And that is from a base that was really not that fast to begin with.

And beyond the actual approval times, particularly on these more complex devices, we are finding a terrible difficulty. Our companies are finding terrible difficulty in getting in to see FDA so they can even agree on a protocol so they can do the clinical studies necessary to support an application.

I have been around this industry for many, many years, first with Senator Kennedy and then in my current capacity. And I have never—in talking to the companies, I have never seen the degree of angst and upset that we have right now. You always have a certain amount of griping between the regulated industry and the regulators. But it is really immense right now, and I think that FDA

recognizes the problem and is working hard to do something about it. But it really does need to be fixed.

Senator NELSON. Is there earlier testimony on the record as to the increased cost as a result of these delays?

Dr. NEXON. We don't have a solid cost estimate of the change. The closest thing we have got is the Makower study, which we would be happy to submit for the record, that tries to do some estimates of the cost of the additional time that FDA takes, imposes on companies.

But there are some—it is a difficult question to answer in terms of cost.

Senator NELSON. Dr. Maisel.

Dr. MAISEL. Well, I guess I would take issue with the characterization of our performance as a "severe deterioration" because the numbers simply don't support that. We have continued to meet 95 percent of our MDUFA goals, meeting the time that we have agreed to and industry has agreed to for our device evaluations.

As I mentioned earlier, 90 percent of the time we review 510(k) applications within 90 days, 98 percent of the time within 150 days. Our PMA Tier 1 MDUFA goals, we have met. And so, I agree that the total time to market has increased. FDA's evaluation time has continued to meet its performance goals.

And so, what that speaks to is partially a quality issue. The quality of applications that we receive is sometimes substandard, and that takes time for industry to respond to requests from FDA staff to complete an application appropriately.

There is no question that, for some of the devices, the complexity has increased. And, undoubtedly, that contributes as well.

Dr. NEXON. Well, I think Dr. Maisel made a good point, which is that there is a difference for time on the FDA clock, which is where the current goals are set, which is the time an application is in the hands of the FDA and it has not been sent back to the manufacturer to answer additional questions or provide additional data. The clock stops when that occurs.

From the point of view of the manufacturer, the point of time on the FDA clock isn't really important. It is the time between when you submit the product and the time you get it to market. Now, obviously, FDA often has legitimate questions. But the fact that the total time has risen so dramatically over this time period indicates to me that FDA is being much less consistent in the things it asks manufacturers.

I do believe that the quality—certainly the quality—of our applications could be improved in many cases, but I don't believe that the quality of our applications has deteriorated 75 percent since 2007.

Senator NELSON. Thank you, Mr. Chairman.

The CHAIRMAN. Go ahead.

Dr. ZUCKERMAN. Yes, thank you.

I just want to say that I think it is a problem when we talk about performance only in terms of speed of getting something to market. And I have criticized FDA, but I want to defend what CDRH has been doing lately. I think they have done a better job of requiring better data.

And Senator Nelson, I happen to know that you have some constituents in the audience today who have been harmed by medical devices, and in the same way that you have constituents who make medical devices in your State, you have a lot of patients who use them.

So I think, when we talk about performance, and I am sure you will agree, we need to talk not just the speed of getting things to market, but making sure they are safe when they get there.

Senator NELSON. And is their testimony being recorded in some way through some of you all, Ms. Zuckerman?

Dr. ZUCKERMAN. I am sorry. I don't understand the question.

Senator NELSON. You spoke of people in the audience who have been harmed by these devices.

Dr. ZUCKERMAN. Yes.

Senator NELSON. Has their matter been presented in some of the testimony here?

Dr. ZUCKERMAN. It hasn't been presented as testimony, but I am happy to provide it for the record.

Senator NELSON. Please.

Dr. ZUCKERMAN. I am very happy to do that.

Thank you.

Senator NELSON. Thank you.

The CHAIRMAN. Senator Blumenthal, will you have another comment or question?

Senator BLUMENTHAL. I do. Thank you, Mr. Chairman.

In fact, I have a whole—I have a ton of questions and interest in areas that I think really need scrutiny. In particular, let me name a few, and I am going to follow up after this hearing with this panel. And each of you has added very importantly to our knowledge and really just want to thank every one of you for being here.

But going back to the doctor who treated Katie, and I don't mean him in particular, I mean the doctors who use these devices. To what extent are, number one, relationships, financial relationships, consulting relationships an important factor for us to consider in decisions by that doctor to use a device that at some point either is of doubtful value, in his view, or questionable value or is simply of equal value.

In other words, to what extent do the financial incentives, sometimes hidden, sometimes not so hidden, factor? And second, off-label marketing clearly a problem. What do we do about it?

So those are two areas I am going to sort of invite your observations on them, and I apologize for sort of tossing a big question at the end of the hearing, two big questions.

Dr. ZUCKERMAN. I could just say that some of the companies, some of the largest companies, including Johnson & Johnson, which makes the DePuy implant, have been penalized by the Justice Department for kickbacks. Kickbacks are kickbacks. Sometimes it is unclear whether funding is a consulting fee or a kickback. But in this case, they were found guilty of kickbacks. So that is something.

I also had a hip replacement. I also have a DePuy hip. I am happy to say not the same kind. Mine hasn't been recalled, yet. But I was able to look up my doctor, thanks to the Sunshine Act, and

I was able to find that my doctor did not get any money, at least listed, from the company.

But one of the problems is there are legitimate fees that can be provided and there are kickbacks, and there is a lot in between. But we know from research, and there is a lot of good research on this, that, when doctors have consulting relationships and financial relationships with companies that make the product that they prescribe, they are more likely to prescribe them, sometimes to the detriment of patients.

So the Justice Department has actually been doing a very good job of going after this in the last few years, more so than previously. But there is that gray in-between area where doctors can get research funds, or consulting fees, that may be legitimate. We know that speaker fees are very often just disguised ways of providing support for doctors who will then like your company and prescribe your products.

Senator BLUMENTHAL. Dr. Resnic.

Dr. RESNIC. I think this is a really critical issue that you bring up and gets to sort of the fundamental question of sort of the necessary trust in the physician-patient relationship. And I work in interventional cardiology, which is heavily device oriented, and it is a significant problem I think in ways that Katie, our patient who testified earlier, described.

She doesn't know if the relationship between her doctor and the manufacturer in any way impaired or affected the judgment of the doctor to use the device. But he probably doesn't either. At best, he doesn't know whether it affects. At worst, he knows and doesn't admit that it might. And I think that this is something that the professional societies in each of the specialties needs to address in concordance with the legislative efforts and programs like the Sunshine Act.

I do think, as a patient advocate, I would not want to find out that my family member or myself treated by a doctor, I would wonder whether their decision-making was some way impaired. Having said that, I think we have to be careful to not throw the baby out with the bath water completely, and there are important relationships, I think, that device innovation requires the clinical feedback from practitioners. But these should be very transparent and out for patients to see as well.

And my institution and the medical school where I work require this, such that we do need to tell our patients about any relationships that we may have, and I think that that is probably what needs to evolve. But it is a sort of ugly underbelly of medicine is these potential relationships.

Senator BLUMENTHAL. Yes?

Mr. HALL. You also asked a question about off-label use, which is a very interesting and complex question. In many situations, off-label use is actually the standard of care and what any patient would want. And, in fact, Congress has recognized that by explicitly talking about the legality of off-label use of medical devices.

And this also raises questions of transparency and patient benefit when often the manufacturer has the most information because the company is in receipt of information from patients, from studies, whatever, and you have this perfectly legal and often very ap-

propriate use taking place in the field for patient benefit. And how do you allow the transmission of information on clinical use, risk, benefits, whatever, when the use is standard of care, but off-label?

Senator BLUMENTHAL. I appreciate your comment, Mr. Hall. But actually, I think my reference was to off-label marketing. Off-label use is perfectly legal and may be appropriate in the view of the treating physician. Off-label marketing is against the law, and for good reason.

Mr. HALL. Correct. What I was trying to point out, perhaps not articulately enough, is that there is this interesting balance between what is marketing and what is providing important clinical, scientific information for the benefit of the patient and the physician in that use.

Senator BLUMENTHAL. Right.

Mr. HALL. And that is what I was trying to reference.

Senator BLUMENTHAL. Mr. Nexon.

Dr. NEXON. The issue of consulting is a very complex one in the device area because the development and improvement of device is so intertwined with medical practice. Many, if not most, devices are initially invented by physicians so that there are obviously royalty arrangements.

All companies, because there is this—devices typically have an 18- to 24-month lifecycle, and then an improved version comes along, and that improved version is based on feedback from practicing physicians. So there are a lot of legitimate consulting and royalty arrangements.

AdvaMed has put forward what I think is a very rigorous code of ethics, which we would be happy to share with you, that lists what we think is permissible payments and what is impermissible. And, of course, we were proud to support Senator Kohl's Sunshine Act, which provided for full disclosure of any payment, whether legitimate or illegitimate, to physicians. But it is a difficult problem.

On off-label use, as you said, off-label promotion is illegal, and companies shouldn't do it.

Senator BLUMENTHAL. And again, I want to thank all of you for your testimony and come back to the comment that Dr. Resnic made. Full disclosure, transparency are very important, and your hospital may require it. I am not sure whether Massachusetts law also requires it. But in many instances, the law fails to provide for—in my view at least—fails to provide for adequate and full disclosure.

So the physician knows in advance that that hip implant is being used by a physician who has some relationship. It may be a speaker's fee. It may be consulting. It may be royalties. But one way or the other, the patient deserves to know, I think.

Dr. RESNIC. I agree. I think Massachusetts did enact in 2009—

Senator BLUMENTHAL. Right.

Dr. RESNIC [continuing]. One of the most stringent public disclosure requirements, as well as prohibition of certain relationships between industry and physicians, both for pharmaceutical device, any medical product. And then within those stringent guidelines, there are certainly institutions that have had their share of challenges and that have moved beyond even the restrictions that Massachusetts has imposed.

There is, in fact, there is always some sort of pendulum or balance in the equation. The one thing that I am concerned about with ever-increasing stringency of relationships, which I think is not a good thing between physicians and industry, is the potential loss for education and even participation by those physicians in the appropriate feedback of clinical insight to medical device manufacturers.

It is just a hard balance. We talked at the beginning of the meeting about the critical balance that FDA needs to strike between safety and innovation. These types of questions also need to strike a balance. Clearly, transparency is paramount, but through transparency, if it is unbalanced, that is, if it is only Massachusetts that stands alone, then device manufacturers tend to move elsewhere.

And I think that perhaps there needs to be more national recommendations regarding these relationships and transparency, as Mr. Kohl's Sunshine Act has recommended and implemented.

Senator BLUMENTHAL. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Senator Blumenthal.

Thank you so much for being here today. And this has been a great panel. You have given us excellent testimony from several different points of view, which is extremely helpful.

We all agree that the FDA must make patient safety a number-one priority, but also we want to do that without stifling innovation. And I think we all believe that we can find a balance. That is what we are here to do.

We are encouraged by the numerous initiatives that FDA is implementing for more effective medical device approval and postmarket surveillance. However, we are still concerned that the agency's oversight of medical products remains on the GAO's high-risk list more than two years now after earning that infamous designation, and that is not acceptable.

We intend to keep a close eye on how FDA changes the fast-track approval process. We will also be monitoring improvements that have been promised by the agency and the industry to better track devices and speed the removal of defective or failed devices from the market.

We are particularly concerned about high-risk devices being fast-tracked. FDA has had over 20 years to tackle these high-risk devices. As we have seen with the Johnson & Johnson hip implant today, it is past time to protect patient safety and correctly classify these devices.

I also believe that the FDA needs to develop a more robust postmarket surveillance program and improve its management of recalls.

We thank you all for being here today. We look forward to continuing this dialogue in the public interest.

Thank you so much for coming.

[Whereupon, at 4:00 p.m., the hearing was adjourned.]

APPENDIX

Testimony of Katherine Korgaokar
Senate Committee on Aging
April 13, 2011

Chairman Kohl, Ranking Member Corker, and Members of the Committee, I thank you for giving me the opportunity to testify today. I am here to give a patient's perspective of what happens when a defective medical device is released to the public. Specifically, I was one of the 96,000 unlucky people who received the DePuy ASR prosthetic hip that was recently recalled in August 2010.

The reason I needed a new hip was because I was born with a congenital condition known as Perthes disease. This disease caused the premature deterioration of bones in my hip joint. Beginning in my early 30s I began experiencing extreme hip pain on a fairly regular basis and had trouble with mobility. Eventually, the pain in my hip became so unbearable that I consulted with an orthopedic surgeon to see if there was anything he could do to relieve my symptoms. The surgeon recommended total hip replacement surgery.

Prior to my operation, my surgeon and I discussed the type of hip that he would use. He told me that it was a new, state-of-the-art metal on metal hip that was specifically designed for young active people such as myself. He told me that the metal on metal design was superior to other designs and that it should last at least 20 years or more. The new state-of-the-art hip that my surgeon used in my surgery was the DePuy ASR hip replacement system.

The initial hip replacement surgery was a huge success. Within three months of the surgery I was essentially pain free and was able to engage in activities that had previously been off limits. The surgery truly changed my life.

Three years later, I met my husband and we were married. Both my husband and I had always wanted to have children and immediately began trying to start a family. However, about eight months later, our plans changed.

At this time, I received a letter from my surgeon advising me that the hip he had put in my body four years prior had been recalled. He told me that I needed to come in for an appointment so that he could examine the hip. When I heard this news I really didn't understand the implications of what I was being told. In my mind, recalls were for dishwashers and cars; not body parts.

When I met with my surgeon he explained that there was some type of design problem with the DePuy ASR that was causing excessive wear and tear on the metal components of the hip. As a result, the hip could be releasing metal debris into my body. My doctor told me I needed to have a blood test performed to see if I had excessive levels of cobalt and chromium. I was told that these are two of the metals used to make the hip. If the levels of these metals were elevated, this meant there was excessive wear and tear occurring in my hip.

A few weeks later my doctor called to tell me that the blood tests showed that I did have elevated levels of cobalt and chromium in my system. In fact, my levels were about 1,000 % higher than they should be.

At that time, I became very concerned. I had no idea how these metals would effect my body, and more importantly, I didn't know if they would impact my ability to have children.

After speaking with my doctor about these concerns, I learned that research had shown that excessive levels of cobalt in the blood could potentially impact the development of a fetus. I also learned that excessive levels of cobalt and chromium had been linked to several serious health conditions such as cancer and cardiomyopathy. As a result, my doctor recommended that I have the hip replaced as soon as possible.

In January 2011, I underwent my second hip replacement surgery. This time, the surgeon installed a more traditional hip with a polyethylene liner in the cup.

The recovery from this second operation has been substantially more difficult than my first. The pain is much worse and it has been extremely difficult to get around. Only recently has my mobility improved to the point where I no longer need crutches. For the past three months I have essentially been confined to my home trying to get through this.

Going forward, I have serious concerns about how this incident will effect my life. I am told that undergoing a hip revision surgery so soon after my first surgery, will likely result in me experiencing more pain, dislocations, and other problems down the road. This is because each operation affects the muscles, tendons, and bones in the hip and makes the hip less stable. I am also told that as a result of this incident I may have to undergo one or more additional hip operations later in my life that could have possibly been avoided. Most importantly, however, I fear that given the small window I had to start a family, this operation may have forever prevented me from ever having children.

As I learned more about the ASR and the process by which it was approved by the FDA, I was shocked. Prior to this incident, I thought that any medical device that was actually being put into people's bodies had been extensively tested before it was released to the public. I had no idea that devices could be "fastracked" by the FDA with little or no testing. I also assumed that the FDA had systems in place to monitor drugs and medical devices for potential defects so that prompt action could be taken if problems arose. Apparently, this did not happen with the DePuy ASR.

Additionally, I am concerned that the doctors who are actually installing these medical devices may not be fully committed to the wellbeing of their patients. Specifically, I recently learned that the surgeon who recommended that I have the DePuy ASR installed in my body had actually received more than \$600,000 from DePuy in "consulting income." (A Disclosure Statement from the DePuy website showing payments to my surgeon is attached hereto as Exhibit A.) This was never disclosed to me before my

surgery. Although I would like to think these payments had no influence on my doctor's decision to use the ASR, I will always have doubts.

Thank you Chairman Kohl and Ranking Member, Corker for holding this hearing and giving me the opportunity to tell my story. I truly hope that you and your colleagues take a serious look at how medical devices are approved in this country and take whatever steps are needed to make sure incidents like this do not happen again.

United States Government Accountability Office

GAO

Testimony
Before the Special Committee on Aging,
U.S. Senate

For Release on Delivery
Expected at 2:00 p.m. EDT
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MEDICAL DEVICES

FDA's Premarket Review
and Postmarket Safety
Efforts

Statement of Marcia Crosse
Director, Health Care



GAO-11-556T



Highlights of GAO-11-556T, a testimony before the Special Committee on Aging, U.S. Senate

April 13, 2011

MEDICAL DEVICES

FDA's Premarket Review and Postmarket Safety Efforts

Why GAO Did This Study

The Food and Drug Administration (FDA) is responsible for overseeing medical devices sold in the United States. In general, new devices are subject to FDA review via either the 510(k) premarket notification process, which determines if a device is substantially equivalent to another legally marketed device, or the more stringent premarket approval (PMA) process, which requires the manufacturer to supply evidence providing reasonable assurance that the device is safe and effective. FDA also has broad responsibilities for postmarket surveillance of devices, including oversight of recalls. A recall involves the correction or removal of a product from the market and is an important remedial action that can mitigate the risks associated with a defective or unsafe medical device. In recent years, GAO has identified a wide variety of concerns related to FDA's ability to fulfill its mission of protecting the public health and added FDA's oversight of medical products, including devices, to its list of high-risk areas.

This statement provides an update on FDA's actions in response to a recommendation made in GAO's report, *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, January 15, 2009). It also contains preliminary information on FDA's oversight of medical device recalls. Because of the preliminary nature of this work, GAO is not making recommendations at this time.

View GAO-11-556T or key components. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA has begun to take steps to address GAO's 2009 recommendation about high-risk devices that are allowed to enter the U.S. market through the less stringent 510(k) process, but progress has been limited. High-risk devices include those which are implantable or life sustaining. In 2009, GAO recommended that FDA expeditiously take steps to issue regulations for the device types classified as high risk that are currently allowed to enter the market via the 510(k) process. Since then, FDA has set strategic goals to address these device types, but has issued a final rule regarding the classification of only one device type. As of April 1, 2011, FDA's action on the 26 remaining types of high-risk devices was incomplete. Thus, these types of devices—such as automated external defibrillators and implantable hip joints—can still enter the U.S. market through the less stringent 510(k) process. GAO found that, since its report was issued in January 2009, FDA has cleared at least 67 510(k) submissions that fall within these high-risk device types. FDA has taken some additional steps to enhance premarket device safety since GAO's 2009 report was issued—for example, it commissioned the Institute of Medicine to conduct an independent review of the premarket review process—but it is too early to tell whether any forthcoming changes will enhance public health.

GAO's preliminary analysis shows that, from 2005 through 2009, firms initiated 3,510 voluntary medical device recalls, an average of just over 700 per year. Although FDA maintains extensive information on each recall, it has not been routinely analyzing recall data that would allow it to explain trends in recalls over time, thus missing an opportunity to proactively identify and address the risks presented by unsafe devices. GAO's preliminary work also identified several gaps in the medical device recall process that limited recalling firms' and FDA's abilities to ensure that the highest-risk recalls were being implemented in an effective and timely manner. GAO found that firms frequently were unable to correct or remove all devices subject to the highest-risk recalls. GAO's preliminary findings indicate that FDA lacks clear guidance for overseeing recalls which has led to inconsistencies in FDA's assessments of whether individual recalls were implemented effectively. Consequently, FDA officials examining similar situations sometimes reached opposite conclusions regarding whether recalls were effective. In addition, FDA had not established thresholds for assessing whether firms effectively completed recalls by correcting or removing a sufficient number of recalled devices. Further, GAO determined that FDA's decisions to terminate completed recalls—that is assess whether firms had taken sufficient actions to prevent a reoccurrence of the problems that led to the recalls—were frequently not made within its prescribed time frames. Finally, GAO found that FDA did not document its justification for terminating recalls. Taken together, GAO's preliminary work suggests that the combined effect of these gaps may increase the risk that unsafe medical devices could remain on the market.

United States Government Accountability Office

Chairman Kohl, Ranking Member Corker, and Members of the Committee:

I am pleased to be here today as you examine issues related to medical device safety. Americans depend on the Food and Drug Administration (FDA) to ensure that medical products sold in the United States are safe and effective. FDA's responsibilities begin before a new device is brought to market and continue after its clearance or approval. Among other things, FDA reviews thousands of submissions for new devices filed each year to decide whether they should be allowed to be marketed in the United States. FDA is also responsible for oversight of thousands of devices already on the market.

In general, unless exempt by regulation, new devices are subject to FDA premarket review via either the 510(k) premarket notification process, to determine whether a new device is substantially equivalent to another legally marketed device, or the more stringent premarket approval (PMA) process, which requires the manufacturer to supply evidence providing reasonable assurance that the device is safe and effective. In addition to its premarket duties, FDA also has broad responsibilities for postmarket surveillance of thousands of devices already on the market, including overseeing recalls. A recall involves the correction or removal of a product from the market and is an important remedial action that can mitigate the risk of serious health consequences associated with a defective or unsafe medical device.

Over the last several years we have identified a wide variety of concerns related to FDA's ability to fulfill its mission of protecting the public health, including weaknesses in FDA's premarket review and postmarket surveillance activities related to medical devices.¹ As a result, FDA's oversight of medical products was added to our list of high-risk areas in 2009 and was also included on our 2011 update of this list.²

¹See "Related GAO Products" at the end of this testimony.

²We regularly report on government operations that we identify as high risk, due to their greater vulnerabilities to fraud, waste, abuse, mismanagement, or the need for transformation to address economy, efficiency, or effectiveness challenges. See GAO, *High-Risk Series: An Update*, GAO-09-271 (Washington, D.C.: Jan. 2009); and GAO, *High-Risk Series: An Update*, GAO-11-278 (Washington, D.C.: Feb. 2011).

In January 2009, we reported on concerns with FDA's premarket review of medical devices.³ Specifically, we found that a significant number of high-risk devices—including device types that FDA has identified as implantable; life sustaining; or posing a significant risk to the health, safety, or welfare of a patient—were cleared for the U.S. market through FDA's less stringent 510(k) review process. We recommended that FDA expeditiously take steps to ensure that high-risk device types are approved through the agency's more rigorous PMA review process. More recently, we have turned our attention to postmarket surveillance and are currently conducting work assessing FDA's oversight of medical device recalls.

My remarks today will focus on concerns that we previously raised regarding the 510(k) process and will include an update on the steps FDA has taken in response to the recommendation contained in our January 2009 report. I will also share our preliminary findings from our ongoing work related to FDA's oversight of the medical device recall process.

For this statement, we interviewed FDA officials and reviewed pertinent statutes, regulations, *Federal Register* notices, and other documents. To determine the steps FDA has taken in response to our 2009 recommendation, we analyzed information from FDA databases⁴ and obtained information on actions taken from FDA's Web site and FDA officials. For our ongoing work on medical device recalls, we obtained information from FDA's Recall Enterprise System on all voluntary recalls initiated and reported to FDA from January 1, 2005, through December 31,

³See 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).

⁴We analyzed information from FDA's product code classification database to identify class III device types that can be cleared for the U.S. market through the 510(k) process and analyzed information from that database as well as FDA's premarket notification 510(k) database to identify traditional and abbreviated 510(k) submissions for class III devices that FDA cleared for the U.S. market since we issued our report on January 15, 2009. Our analysis did not include certain types of device submissions, for example, special 510(k) submissions, which are requests for clearance of minor modifications to devices that have already been cleared through the 510(k) process. Because related devices can be "bundled" together in a single submission, one submission may include one or more devices.

2009.⁵ We then used this information to determine, among other things, the number of recalls initiated per year; the number of recalls by recall risk levels; and status of the recalls. In addition, we examined FDA's oversight of 53, or 40 percent, of all high-risk recalls that were initiated from January 1, 2005, through December 31, 2009. For each of these 53 recalls, we obtained and reviewed the case files which documented firms' and FDA's actions. We reviewed key documents such as information from the firms on the causes of the recalls, the firms' actions to prevent reoccurrence of similar problems, the recall notifications firms sent out to customers, and FDA's correspondence with firms. As part of our review, we reviewed whether firms and FDA followed FDA's procedures for implementing and overseeing the recalls. We determined that the data we used for our report were sufficiently reliable for our purposes. We received technical comments on a draft of this statement from FDA, which we incorporated as appropriate.

We conducted our work related to FDA's premarket review of medical devices and our update of that work in accordance with generally accepted government auditing standards.⁶ Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives. We are also conducting our work on FDA's oversight of medical device recalls in accordance with generally accepted government auditing standards.⁷ Because of the preliminary nature of this work, we are not making recommendations on FDA's recall process at this time.

⁵While FDA has authority to order a mandatory recall, it did not exercise this authority during the period we reviewed. See 21 U.S.C. § 360h(e), 21 C.F.R. pt. 810 (2010). Also, our information does not include devices that a firm may have voluntarily taken off the market for other, less serious, reasons. For example, a market withdrawal is a firm's correction or removal of a distributed device that involves no violation or a minor violation of the laws FDA administers and for which FDA would not initiate legal action. 21 C.F.R. § 806.3(h) (2010).

⁶We conducted the work for our 2009 report, GAO-09-190, from March 2008 to January 2009. We conducted the work to update FDA actions taken in response to that report's recommendation from January 2011 to April 2011.

⁷We began conducting this work in January 2010 and our work is ongoing.

Background

FDA classifies each device type into one of three classes based on the level of risk it poses and the controls necessary to reasonably ensure its safety and effectiveness.⁸ Examples of types of devices in each class include the following:

- class I: tongue depressors, elastic bandages, reading glasses, and forceps;
- class II: electrocardiographs, powered bone drills, and mercury thermometers; and
- class III: pacemakers and replacement heart valves.

Premarket Review of Medical Devices

Before medical devices may be legally marketed in the United States, they are generally subject to one of two types of FDA premarket review, unless exempt by FDA regulations.⁹ These reviews are:

- **Premarket approval or PMA process:** The manufacturer must submit evidence, typically including clinical data, providing reasonable assurance that the new device is safe and effective. The PMA process is the most stringent type of premarket review. A successful submission results in FDA's approval to market the device.
- **Premarket notification or 510(k) process:** Premarket notification is commonly called "510(k)" in reference to section 510(k) of the Federal Food, Drug, and Cosmetic Act, where the notification requirement is listed. The manufacturer must demonstrate to FDA that the new device is

⁸FDA's classification of device types is codified in parts 862 through 892 of title 21 of the Code of Federal Regulations (2010). Class I devices are those for which compliance with general controls, such as good manufacturing practices specified in FDA's quality system regulation, is sufficient to provide reasonable assurance of their safety and effectiveness. Class II devices are subject to general controls and may also be subject to special controls, such as postmarket surveillance. Class III devices are those (1) for which insufficient information exists to determine whether general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device and (2) that support or sustain human life or are of substantial importance in preventing impairment of human health, or that present a potential unreasonable risk of illness or injury. See 21 U.S.C. § 360c.

⁹A small percentage of devices enter the market by other means, such as through the humanitarian device exemption process that allows market entry, without adherence to certain requirements, for devices benefiting patients with rare diseases or conditions. See 21 U.S.C. § 360j(m), 21 C.F.R. pt. 814, subpart H (2010). In addition, many other less risky types of class I and II devices are also exempt from FDA's premarket review.

substantially equivalent to a device already legally on the market that does not require a PMA.¹⁰ For most 510(k) submissions, clinical data are not required and substantial equivalence will normally be determined based on comparative descriptions of intended device uses and technological characteristics, and may include performance data. A successful submission results in FDA's clearance to market the device.

In general, class I and II device types subject to premarket review are required to obtain FDA clearance through the 510(k) process, and class III device types are required to obtain FDA approval through the more rigorous PMA process. With the enactment of the Medical Device Amendments of 1976, Congress imposed requirements under which all class III devices would be approved through the PMA process before being marketed in the United States.¹¹ However, certain types of class III devices that were in commercial distribution in the United States before May 28, 1976,¹² (called preamendment device types) and those determined to be substantially equivalent to them may be cleared through the less stringent 510(k) process until FDA publishes regulations requiring them to go through the PMA process or reclassifies them into a lower class.¹³ Between 1976 and 1990, FDA issued regulations requiring some class III device types to go through the PMA process, but many class III device types continued to be reviewed through the 510(k) process. The Safe Medical Devices Act of 1990 required FDA (1) to re-examine the preamendment class III device types for which PMAs were not yet required to determine if they should be reclassified to class I or II or remain in class III and (2) to establish a schedule to promulgate regulations requiring those

¹⁰*Substantial equivalence or substantially equivalent* means that the device has the same intended use as another legally marketed device and the same technological characteristics, or that the device has different technological characteristics and information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device and does not raise different questions of safety or effectiveness. 21 U.S.C. § 360c(i)(1)(A).

¹¹See Pub. L. No. 94-295, § 2, 90 Stat. 539, 552-59 (codified at 21 U.S.C. § 360e).

¹²May 28, 1976, is the date of enactment of the Medical Device Amendments of 1976, which established the three device classes.

¹³FDA may, by regulation, change the classification of a device from class III to (1) class II if it determines that special controls would provide reasonable assurance of the safety and effectiveness of the device and that general controls alone would not provide reasonable assurance of the safety and effectiveness of the device or (2) class I if FDA determines that general controls alone would provide reasonable assurance of the safety and effectiveness of the device. 21 U.S.C. § 360c(e).

preamendment device types that remain in class III to obtain FDA approval through the PMA process.¹⁴ Accordingly, all class III devices are eventually to be reviewed through the PMA process.

In our January 2009 report, we found that although Congress envisioned that all class III devices would be approved through the more stringent PMA process, the agency's actions to make this the case were incomplete. We found that in fiscal years 2003 through 2007, FDA continued to clear submissions for class III devices through the less stringent 510(k) process—clearing 228 over the 5-year period. We recommended that FDA expeditiously take steps to issue regulations for each class III device type allowed to enter the market through the 510(k) process, including to (1) reclassify each device type into class I or class II, or requiring it to remain in class III, and (2) for those device types remaining in class III, require approval for marketing through the PMA process. FDA agreed with our recommendation when we issued our report, but did not specify time frames in which it would take action.

Postmarket Oversight of Voluntary Medical Device Recalls

Overseeing recalls is an important element of FDA's postmarket responsibilities. FDA defines a recall as a firm's removal or correction of a marketed product that FDA (1) considers to be in violation of the laws it administers, and (2) against which the agency would initiate legal actions.¹⁵ Nearly all medical device recalls are voluntarily initiated by a recalling firm, usually the manufacturer of the device. To initiate a voluntary recall, a firm notifies those who have received, purchased, or used the device. The firm may be asked to provide FDA with information such as the reason for the correction or removal of the device, an assessment of the health hazard associated with the device, and the volume of product in distribution and proposed strategy for conducting the recall.¹⁶ The strategy should contain details on the firm's plan for ensuring that its customers and device users correct or remove the device

¹⁴Pub. L. No. 101-629, § 4(b), 104 Stat. 4511, 4515-17 (codified at 21 U.S.C. § 360e(i)).

¹⁵21 C.F.R. § 7.3(g) (2010). A removal is the physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction, or inspection. A correction may involve these actions without the physical removal of a device from its point of use. See 21 C.F.R. 806.2(d), (i) (2010).

¹⁶The firm will contact one of FDA's district offices depending upon the location from which it chooses to manage the recall. This district will have primary responsibility for monitoring the recall. Each district has a recall coordinator, who, among other duties, processes medical device recalls and monitors the progress of the firm's actions.

according to the firm's instructions. FDA's role is generally to oversee a firm's management of a recall. As part of its oversight, FDA reviews and recommends changes to the recall strategy and assigns one of three recall classifications—class I, II, or III—to indicate the relative degree of health hazard posed by the product being recalled. For a class I recall, FDA has determined that there is a reasonable probability that use of, or exposure to, the product could cause serious adverse health consequences or death. Class II recalls are those for which FDA has determined that the use of, or exposure to, the product could cause temporary or medically reversible adverse health consequences or that the probability of serious adverse health consequences is remote. For class III recalls, FDA has determined that use of, or exposure to, a device is not likely to cause adverse health consequences. FDA advises the recalling firm of the assigned recall classification; and posts information about the recall in its weekly enforcement report.

It is important to note that FDA's device and recall classification schemes carry opposite designations. The potential degree of health risk associated with device classes is designated from class III (high) to class I (low), while the potential risk associated with recall classes is designated from class I (high) to class III (low).

FDA also monitors the progress of a recall and verifies whether the recalling firm has effectively implemented the recall strategy. FDA requests that a recalling firm periodically provide the monitoring district with status reports that provide updates on the progress of recalls. FDA district staff also conduct audit checks to confirm that the recalling firm has properly corrected or removed devices from the market, in accordance with the recall strategy. Once the firm believes it has completed the recall—that is, done everything as outlined in the recall strategy—it should submit a recall termination request to the monitoring district office. As part of the termination decision, FDA should assess whether the firm has taken sufficient corrective actions to prevent a recurrence of the problem that led to the recall. For class I recalls, FDA district staff review a firm's request, and if they agree, send a recall termination request to headquarters. For class II and III recalls, FDA district staff make the final termination decision. According to FDA's procedures, FDA should terminate a recall within 3 months after the firm completes the recall.

**FDA Has Taken Some
Actions in Response
to Our
Recommendation to
Strengthen the
Premarket Review
Process, but Concerns
About the 510(k)
Process Remain**

FDA has begun to take steps to address our 2009 recommendation about class III devices that are still allowed to enter the U.S. market through the less stringent 510(k) process, but progress has been limited. Concerns persist about the effectiveness of the 510(k) process in general, including its ability to provide adequate assurance that devices are safe and effective. In 2009, we recommended that FDA expeditiously take steps to address class III device types allowed to enter the market via the 510(k) process by issuing regulations requiring submission of PMAs or reclassifying them to a lower class. Since our report was issued, the agency has set strategic goals to address this matter, but has issued a final rule regarding the classification of only one device type.¹⁷ As of April 1, 2011, 26 additional class III device types could still enter the U.S. market through the less stringent 510(k) process.

FDA has been taking steps to address the 26 class III device types—including automated external defibrillators and implantable hip joints—that can still enter the U.S. market through the 510(k) process. Specifically, FDA is following a 5-step process to require PMAs or to reclassify them to a lower device class. As shown in table 1, as of April 1, 2011, FDA was at step 2—assessing the risk and benefits—for 21 device types.¹⁸ FDA was at step 4—receiving and reviewing comments provided on proposed rules—for 5 other device types, but had not yet issued final rules requiring PMAs or reclassifying any of them.¹⁹

¹⁷See 74 *Fed. Reg.* 42773. (Aug. 25, 2009).

¹⁸On April 9, 2009, FDA published a notice in the *Federal Register* requiring manufacturers of 25 of the 26 device types to submit summary information, including adverse safety or effectiveness information, to determine whether to require PMAs or to reclassify the device types. 74 *Fed. Reg.* 16214.

¹⁹FDA published a proposed rule on August 25, 2010, that, if finalized, would retain class III designation and require PMAs for four device types. 75 *Fed. Reg.* 52294. FDA published a proposed rule, regarding classification, for another device type on April 6, 2006. 71 *Fed. Reg.* 17390.

Table 1: Status of FDA Action for 26 Class III Device Types that Can Be Cleared through the 510(k) Process, as of April 1, 2011

Step in FDA process	Number of device types at this step in the process
Step 1: FDA collects existing information, which includes publishing a <i>Federal Register</i> notice to solicit information, and may include holding an FDA advisory panel meeting	0
Step 2: FDA assesses the risks and benefits	21
Step 3: FDA proposes classification into class I, II, or III, which is announced as a proposed rule in a <i>Federal Register</i> notice	0
Step 4: FDA receives and reviews comments provided	5
Step 5: FDA finalizes classification into class I, II, or III, which is announced as a final rule in a <i>Federal Register</i> notice ^a	0

Source: GAO analysis of FDA information.

Note: This table presents the FDA 5-step process and status from the FDA Web site <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHTransparency/ucm240318.htm>, accessed April 1, 2011.

^aFor device types retained in class III, FDA will call for PMA applications and sponsors of devices previously cleared through the 510(k) process will need to submit PMA applications in order to continue to market their devices (with a grace period to permit possible transition to obtaining PMA approval).

While FDA has taken essential initial steps toward implementing our recommendation, until the agency issues final regulations either reclassifying or requiring PMAs for class III device types that currently can be cleared through the less stringent 510(k) process, its actions remain incomplete. Thus, these 26 device types can still enter the U.S. market through the less stringent premarket review process. Since we issued our report in January 2009, FDA cleared at least 67 individual submissions that fall within 12 of these class III device types through the 510(k) process.²⁰

Subsequent to the issuance of our 2009 report and in response to numerous concerns over the effectiveness of the 510(k) process, including its ability to provide adequate assurance that devices are safe and effective, FDA announced it would take additional actions to enhance

²⁰Our analysis did not include special 510(k) submissions, which are requests for clearance of minor modifications to devices that have already been cleared through the 510(k) process.

premarket device safety. In 2009, FDA reported that it would conduct its own comprehensive internal assessment of the premarket medical device approval process and commissioned the Institute of Medicine to conduct an independent review to assess whether the 510(k) process sufficiently protects patients and promotes public health. The Institute of Medicine is expected to issue its report in mid-2011.

Shortcomings in FDA's Oversight of the Highest-Risk Medical Device Recalls Increase the Risk That Unsafe Devices Continue to Be Used

Our preliminary findings suggest that shortcomings in FDA's oversight of the medical device recall process may limit the agency's ability to ensure that the highest-risk recalls are being implemented in an effective and timely manner. These shortcomings span the entire range of the agency's oversight activities—from the lack of a broad-based program to systematically assess trends in recalls, to inconsistencies in the way FDA ensures the effective completion of individual recalls.

FDA Has Not Routinely Used Recall Data to Aid Its Oversight of the Recall Process

Although FDA's recall data system contains numerous data elements that would allow for analyses of recall data, our preliminary findings suggest that FDA is not using this system to effectively monitor and manage its recall program. This system contains information on, for example, the status of each recall (e.g., ongoing or terminated); the reason for the recall; the specific device being recalled; the recall classification level assigned based on FDA's assessment of risk; the dates the recalls were initiated, classified, and terminated; and the medical specialty—area of use—for each device subject to recall (e.g., cardiovascular or orthopedic). However, FDA has not routinely used these recall data as a surveillance tool or for examining broad trends of medical device recalls.²¹ Instead of using this information to conduct systemic analyses of the recall program, which would be consistent with the agency's strategic goal of improving the quality and safety of manufactured products in the supply chain, FDA has primarily been using data from its recall system for processing individual recalls.

²¹We previously reported on the importance of establishing and using metrics as a management tool. See, for example, GAO, *Food and Drug Administration: Opportunities Exist to Better Address Management Challenges*, GAO-10-279 (Washington, D.C.: Feb. 19, 2010).

Our preliminary analysis showed that between January 1, 2005, and December 31, 2009, firms initiated 3,510 device recalls. Only a small percentage of these recalls—about 4 percent—were classified by FDA as class I recalls—those that pose a reasonable probability that the use of, or exposure to, these products will cause serious adverse health consequences or death. The vast majority—nearly 83 percent—were classified by FDA as class II recalls, meaning use of, or exposure to, these devices may cause temporary or medically reversible adverse health consequences or that the probability of serious adverse health consequences is remote; and about 14 percent were classified as class III recalls, which pose the lowest risk.

Based on our preliminary analysis, we provided key summaries to FDA officials and asked them to comment on trends that we observed. Officials indicated that they have not fully analyzed these data and could not explain trends without extensive research of individual case files. For example, they could not explain why the majority of recalls are class II, why class I recalls more than doubled between 2008 and 2009, or why many recalls had been ongoing for 5 years. Officials also could not provide definitive answers when we asked them to comment on other related topics, such as:

- trends in the number of recalls over time;
- variation in the numbers of recalls by recall classification levels;
- types of devices and medical specialties of devices accounting for most recalls; and
- length of time needed to complete or terminate recalls.

Although FDA has not been routinely analyzing recall data to assess the effectiveness of the recall process, officials indicated that they have used these data to support compliance and subsequent enforcement actions. For example, officials indicated that they use recall data to help identify which firms the agency should inspect for assessing compliance with laws and regulations.

FDA Inconsistently Assessed the Effectiveness of Recalls

Our preliminary analysis revealed inconsistencies in FDA's assessments of the effectiveness of recalls. A key tool to making these assessments are FDA's "audit checks" in which investigators from FDA's district offices contact a percentage of customers or device users affected by the recall to determine whether they received the recall notice and followed the recalling firm's instructions for removing or correcting the device. However, we identified numerous inconsistencies in the way FDA's investigators implemented these audit checks, resulting in conflicting determinations about whether recalls were effectively conducted.

Our analysis of 2,196 audit check forms associated with the class I recalls we reviewed found a variety of inconsistencies in how the audit checks were implemented and documented for nearly 90 percent of these recalls.²² For each of these recalls we found inconsistencies in how different investigators determined whether a recall was effective or ineffective when conducting their audit checks of recalls. We also identified inconsistencies in the level of detail provided in the audit check report and the level of effort undertaken by different investigators. These recalls covered a wide range of devices, including implantable pumps and automated external defibrillators. For example, when conducting audit checks, some investigators concluded that recalls were effective, despite noting problems (such as device users not following the firm's instructions), while other investigators concluded under similar circumstances that recalls were ineffective. In other recalls, some investigators noted actions they took when they discovered problems, such as providing the device users with a copy of the recall notice or instructing them on actions to take in order to implement a recall. In contrast, other investigators did not indicate whether they made any attempt to help the user implement the recall.

FDA officials at both headquarters and the district offices we contacted acknowledged that there are no detailed instructions or requirements for conducting audit checks and that there can be inconsistencies in the process. They also agreed that this may be an area where enhanced guidance is needed.

²²FDA's regulatory procedures note that audit checks should be conducted for all class I recalls. FDA conducted audit checks for 45 of the 53 class I recalls (85 percent) we reviewed. In six of the eight cases in which FDA did not conduct audit checks, the recall file contained written documentation explaining why audit checks were not conducted.

FDA Lacks Specific Criteria to Determine Whether Firms Have Taken Adequate Steps to Correct or Remove Recalled Devices

One of the gaps in FDA's recall process suggested by our preliminary work is that FDA lacks specific criteria for making decisions about whether recalling firms have effectively completed their recalls by taking adequate steps to correct or remove recalled devices. Our preliminary review of FDA's recall procedures found that the procedures do not contain any specific criteria or general guidelines governing the extent to which firms should be correcting or removing various types of devices—such as a benchmark recall rate—before a recall should be considered completed. FDA officials indicated they consider a recall complete when a firm has completed actions outlined in its recall strategy. In particular, they evaluate whether firms completed their assigned level of effectiveness checks, and have corrected or removed recalled devices in “an acceptable manner.” However, FDA officials said that they do not have specific criteria or thresholds concerning the proportion of various types of devices that firms should be able to correct or remove.

Our preliminary review shows that firms are not always able to correct or remove all unsafe medical devices from the market. Of the 53 class I recalls we reviewed, we found 10 were ongoing, 14 were completed—meaning that FDA district office officials concluded that the firm had fulfilled its responsibilities for correcting or removing the devices—and 29 were terminated—meaning that FDA headquarters determined that recalling firms had taken sufficient corrective actions to prevent reoccurrence of the problems that led to the recalls.²³ Of the 43 recalls in our sample that were either completed or terminated, we found that for 20, or 47 percent of these recalls, firms were able to correct or remove all products. However, we found that in the other 23 recalls, or 53 percent, firms were unable to correct or remove all products. These recalls ranged widely, in both volume of devices subject to recall and the types of devices being recalled. Some recalls involved hundreds of thousands of disposable products, while others involved a small number of life-sustaining implantable devices. Recalling firms were often unable to correct or remove all devices. This was because firms either could not locate some of the customers or device users, or these customers or device users could not locate the devices subject to recall. In other cases, devices could not be corrected or removed because they were sold at retail outlets (such as glucose test strips) to individuals who may not have known about the

²³We obtained the current status of these recalls through our reviews of the recall files and discussions with FDA district office officials. These discussions took place between December 2010 and February 2011.

recall. For example, in a recall of tracheal tubes included in certain pediatric medical kits, 1,400 tubes had been distributed but only 200 were returned to the recalling firm. The firm said that the rest had likely been used.

FDA's Recall Termination Process Is Compromised by Weak Procedures and May Result in Recalled Medical Devices Remaining on the Market

Our preliminary findings also suggest another gap in the recall process—insufficient documentation justifying FDA's termination decisions. Without such documentation, we were unable to assess the extent to which FDA's termination process appropriately evaluated recalling firms' corrective actions. Although FDA requests that firms submit corrective and preventive action plans for review and approval before a recall can be terminated, we found little documentation regarding how FDA assessed whether such plans were sufficient when it terminated recalls. When we asked to review documentation justifying the decisions for the 29 terminated recalls in our sample, FDA officials indicated that they do not maintain extensive documentation justifying the basis for their termination decisions. They told us that creating documentation to support concurrence with the termination recommendation is not part of past or current termination procedures. This approach is inconsistent with internal control standards for the federal government, which indicate "that all transactions and other significant events need to be clearly documented," and stress the importance of "the creation and maintenance of related records which provide evidence of execution of these activities as well as appropriate documentation."²¹

Also, we found that FDA termination decisions were frequently not made in a timely manner—within 3 months of the completion of the recall—increasing the risk that unsafe or defective devices remained available for use. Of the 53 recalls in our sample, 29 were terminated—meaning FDA headquarters agreed with an FDA district office that the firm did not need to take additional actions to prevent reoccurrence of problems that led to the recall. For 72 percent of the terminated recalls, FDA did not make its termination decision within 3 months of the recall's completion, as called for in FDA's regulatory procedures. Overall, termination decisions took on average 180 business days from the completion date, though they ranged from 10 days to 800 days after that date.

²¹See GAO, *Standards for Internal Control in the Federal Government*, GAO-AIMD-00-21.3.1 (Washington, D.C.: Nov. 1999).

We found at least one instance where FDA's failure to make a timely termination assessment allowed for a potentially unsafe product to be re-introduced into the market and used for surgical procedures. In this case, based on adverse event reports that screws in its spinal fixation system were becoming loose post-operatively, the firm decided to recall the device in December 2005. The firm implemented its recall, and removed all devices. The firm indicated that it developed a corrective action plan for the screw problem, and relaunched the device in April 2006. It then requested termination from FDA in May 2006. FDA followed up on this request by leaving three voice mail messages with the firm and received no response. The agency sent out a request for information a year later, in May 2007. In June 2007, the company again indicated that the recall was complete, and requested termination. In September 2007, FDA conducted an inspection of the company's manufacturing facility, and found that while the recall was complete, the corrective action was not adequate. Over the course of the next 2 years, the firm worked with FDA to get revisions to the device approved, but eventually agreed to a second recall for the revised device. This recall was initiated in May 2009. We identified five reports of adverse events related to continuing problems with the implanted device that were filed with FDA subsequent to the firm's relaunch of the device in April 2006. These reports were filed from December 2006 through March 2007, and revealed that in all cases, patients required surgical intervention to correct or remove the device.

While FDA's recent actions to try to improve the premarket approval process are positive steps—such as commissioning the Institute of Medicine to conduct an independent review of the process—it remains to be seen whether these actions will help ensure that medical devices marketed in the United States receive appropriate premarket review. In addition, gaps in FDA's postmarket surveillance shows that unsafe and ineffective devices may continue to be used, despite being recalled. The agency faces a challenging balancing act. While it is important to allow devices on the market to treat patients who need them, it is also essential that FDA take necessary steps to provide a reasonable assurance that those medical devices that do enter the market are safe and effective. Likewise, it is vital that the agency's postmarket safety efforts are both vigorous and timely.

Chairman Kohl and Ranking Member Corker, this completes my prepared statement. I would be happy to respond to any questions you or the other members of the committee may have at this time.

**Contacts and
Acknowledgments**

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**Written Statement of Diana Zuckerman, PhD
President, National Research Center for Women & Families
Before the U.S. Senate Committee on Aging
April 13, 2011**

Thank you for the opportunity to testify about the approval process for medical devices.

I am president of the National Research Center for Women & Families, which is a think tank that uses scientific and medical research to develop strategies to improve the health of adults and children. I am also testifying on behalf of our Cancer Prevention and Treatment Fund, which analyzes research results that can improve the prevention, diagnosis, and treatment of cancer.

My perspective is as a researcher trained in epidemiology and public health at Yale Medical School, who was on the faculty of Vassar and Yale and conducted longitudinal research at Harvard, and is currently a fellow at the University of Pennsylvania Center for Bioethics. I am also a former Congressional staffer for the House subcommittee that has oversight jurisdiction over the FDA, and for the Senate Veterans Affairs Committee.

Our Center does not accept funding from medical device or pharmaceutical companies, so that we have no financial interests in the medical products and policies we examine. I personally have ties to Johnson & Johnson, because my 93-year-old father spent his career there and family members have stock in the company. As a stockholder, I am appalled that J & J paid kickbacks to doctors and failed to adequately test the safety or efficacy of their medical devices, including the one in my left hip.

Our Study of High-Risk Recalls of Medical Devices: 2005-2009

I am the primary author of a recent study of medical device recalls, published in the prestigious peer-reviewed journal the *Archives of Internal Medicine*. Our article was accompanied by an editorial supporting our analysis, written by the journal's editor-in-chief, Dr. Rita Redberg. My study co-authors are Paul Brown of the National Research Center for Women & Families and Dr. Steven Nissen, Chairman of Cardiovascular Medicine at the Cleveland Clinic.

We studied all the recalls between 2005 and 2009 that the FDA designated as the highest risk because they could cause "serious health problems or death." Using the FDA's public databases, our study found that **more than 3 out of 4 of those high-risk recalls were not approved by the FDA's PMA process, but rather were cleared through the much less stringent 510(k) process or were exempt from any review because they were considered so low-risk.** In my testimony today, I will discuss the implications of our findings and make recommendations that will save lives and healthcare dollars and improve the health of millions of Americans, especially our older citizens.

Unlike the PMA process for devices or the IND process for prescription drugs, the 510(k) process does not require testing in patients or pre-market inspections. Ironically, given the lack of clinical trials prior to clearance, post-market studies are never required as a condition of approval.

Prior to publication, I had described the study at a public FDA meeting in February 2010 and at a meeting of the Institute of Medicine in March 2010. Subsequently, Ralph Hall conducted a similar study using the same FDA data set, but came to different conclusions. The largest Medical Device Manufacturers trade group, AdvaMed, paid Battelle Institute to conduct a similar study, with conclusions similar to Hall's.

Our study and the Hall and Battelle/AdvaMed studies were all based on the FDA's high-risk device recalls between 2005 and 2009 or through May 2010, and all concluded that most of the highest-risk recalls had been cleared through the 510(k) process rather than the more stringent pre-market approval (PMA) process. However, the numbers were somewhat different. The Hall study compiled data from various pages on the FDA website on all devices designated as Class I (highest risk) recalls from 2005 through 2009. The Battelle/AdvaMed study compiled data from the FDA website for all devices designated as high-risk recalls from 2005 through May 1, 2010, but then grouped together recalls of products with different model numbers or different trade names.

In contrast, our study took a more conservative approach, by using the FDA's official list of high-risk recalls, which is called the "List of Recalls," for devices recalled from 2005 through 2009 (www.fda.gov/MedicalDevices/Safety/RecallsCorrectionsRemovals/ListofRecalls/default.htm). Rather than including all 115 of the devices on the list, however, we only included the 113 devices that were also on the FDA's list of "Class I recalls," which FDA defines as the highest risk recalls. Deleting those two devices resulted in two fewer 510(k) devices in our study. In addition, we included counterfeit and "other" devices that did not go through any FDA review in the total number of recalls, in an effort to be even more cautious in our interpretation. This lowered the percentage of 510(k) and exempt devices that were among the highest risk recalls to the 78% that we reported in our study, compared to the 81% that Hall reported.

The Battelle/AdvaMed study reported a smaller number of recalls than either our study or the Hall study, because Battelle/AdvaMed grouped together recalls of products with different model numbers or different trade names, and because they excluded devices that had been exempt from FDA review from their statistical analyses. These two methodological decisions reduced the number and percentage of recalled devices in their study that were designated as not approved through the PMA process.

In summary, unlike either of the other two studies, we used the official FDA list of recalls, then made the criteria even more stringent by deleting any devices that the FDA had not designated as Class I (the highest-risk recalls).

What are the Policy Implications of High-Risk Recalls?

The PMA process is similar to the approval process for prescription drugs, and in their review of the process, the GAO criticized the FDA for failing to follow the law when they clear high-risk devices through the 510(k) process. In their January 2009 report, the GAO pointed out that, by law, the FDA has been required to either reclassify Class III (high-risk) devices that are currently going through the 510(k) process as moderate risk (Class II), or require those devices to be reviewed through the PMA process.

Mr. Hall and medical device companies have defended the status quo, saying that the important statistic is the less than 1% of device applications that are later subject to a high-risk recall.

We disagree. In our published study, **we questioned why the FDA would determine that a device can cause death or serious harm when it fails, but not consider that same device high-risk when initially categorizing it for review.** Cardiac devices and general hospital devices were the most common categories of high risk-recalls, including many cleared through the 510(k) process. Although it might be possible for a moderate-risk device to result in a high-risk recall for a completely unpredictable reason, by definition, the vast majority of moderate-risk devices should not have the potential to cause such harm. A defibrillator that fails to work, an implant that breaks inside the human body, or a diagnostic test that is inaccurate are predictable problems that should be considered when the FDA determines whether or not those devices are high-risk. Therefore, the fact that 71 % of high-risk recalls were cleared through the 510(k) process and an additional 7% were never even subject to FDA review indicates inconsistency in the FDA's policies regarding the classifications of risk for review compared to recall criteria.

What are the Public Health Implications of High-Risk Recalls?

Our criticisms of the use of the 510(k) review process for implants and other high-risk devices are based on our public health perspective. The detrimental impact of these defective medical devices on patients and the public health is substantial and could be reduced with relatively small changes in the 510(k) process and how it is implemented. It is substantial because from 2005 through 2009, the 113 highest-risk device recalls involved 112.6 million recalled products. In the first six months of 2010, the FDA recalled more than 437 million additional products because of high risks, including death. That means that in just six months there were 1.4 medical devices recalled for every person living in the U.S.

Some claim that the FDA's standard for a high-risk recall is not very high. The statistics suggest otherwise. There were only 113 high-risk recalls from 2005-2009, compared to 7,884 moderate-risk recalls during those same years. Some of those "moderate-risk" recalls resulted in a need for inpatient surgery and lengthy hospital stays and rehabilitation. For example, the 158 recalls of hip, knee, and ankle implants from 2005 through 2009 were not included in any of the three studies, because the FDA did not consider them high risk-recalls. As you have heard from a patient today, a recalled hip, for example, often requires revision surgery much sooner than expected, and that costs an average of

\$35,000 and results in a 3-5 day hospital stay, at least 6 weeks walking with crutches or a walker or cane, four weeks where the patient is not allowed to drive, and several weeks or months of rehab or physical therapy. Despite the high cost and debilitating impact on patients, which could be even more devastating to elderly patients who lack someone at home to care for them, the FDA did not consider any of the hip and knee recalls from 2005 through 2009 to be high-risk.

The bottom line is that even “moderate-risk” recalled devices can sometimes result in death during surgery, and certainly add billions to Medicare costs when they result in additional surgery and hospitalizations from the complications of defective devices.

The very high number of recalled products, like the low percentage of high-risk recalls, sounds impressive, but neither tells us the human or financial costs of unsafe 510(k) products. The impact on patients’ health and medical costs is impossible to determine, but experts agree that adverse reaction reports, despite their many shortcomings, represent a fraction of the actual harm. The FDA reported 116,086 device-related injuries and 2,830 deaths in just one year (2006). Our analysis of subsequent years indicates much higher statistics. There were almost 5,000 reported deaths in 2009, and the hundreds of thousands of serious complications reported on the FDA web site every year are just the tip of the iceberg, because experts tell us that most doctors don’t report these to the FDA. Hospitals are required to report deaths and serious injuries that might have resulted from medical devices, but doctors are not required to report them to the hospital, and many don’t.

How many of these reported deaths and injuries were caused by devices that were not subject to clinical trials or pre-market inspections, because they were cleared through the 510(k) process? That information is not available.

Industry warns that clinical trials and other requirements of the PMA process take more time and cost more than the 510(k) process. I agree. However, there are no available data on whether lives have been lost because of delays in getting devices to market in the U.S. In fact, by definition, any dramatically innovative medical device should be submitted through the PMA process, not the 510(k) process. The 510(k) process is intended for more incremental changes. Without clinical trials, it is impossible to determine whether those changes save lives.

Moreover, since **Medicare requires that medical devices be proven beneficial in clinical trials**, devices cleared through the 510(k) process will not necessarily be reimbursed by Medicare or insurance companies until clinical trials are completed. That means that the delay caused by PMA criteria such as clinical trials often does not mean a corresponding delay in the widespread use of a device, compared to the 510(k) process. The stricter criteria of Medicare compared to FDA will delay the widespread use for a device that went through the 510(k) process without clinical trials. However, Medicare coverage would not result in the safeguards provided by pre-market inspections or post-market studies.

Pharmaceutical companies do not question the need for clinical trials or pre-market inspections, and the higher standards FDA requires of those companies have not interfered

with pharmaceutical companies' high profits. There is no public health reason for heart valves and other high-risk devices to receive less scrutiny than prescription drugs for relatively minor health problems such as constipation; in fact, the reverse would be more logical. If that is burdensome to smaller device companies, there is no proof that outweighs public health considerations.

Since most devices are cleared through the 510(k) process, is it inevitable that most recalls be 510(k) devices?

Since the proportion of high-risk recalled devices was less than 1% regardless of whether a device was cleared through the 510(k) process or approved through a PMA, does that mean that the current policies of reviewing medical devices work well?

To calculate the percentage of 510(k) devices that were high-risk recalls, Hall's denominator was the *number of all devices that were submitted from 2000 through 2009*, averaged per year and then multiplied by 5 to create a 5-year average. That methodology is incorrect for two reasons:

- **Submissions are not appropriate for use as a denominator** because many devices that were submitted were not cleared, and even those that were cleared were not necessarily ever sold in the U.S. Obviously, a device can't be recalled by the FDA if it is never sold in the U.S. That makes Hall's denominator much too large, and his calculation of the percentage of 510(k) devices that were recalled much too small. His denominator should have been the number of devices that were **cleared** by the FDA and subsequently sold on the U.S. market.
- **Using an average over 10 years to calculate the denominator is incorrect** for several reasons. First, an unknown number of devices that were cleared during the first five years (2000-2004) had already been taken off the market by 2005, when the high-risk recalls started to be evaluated for this study. Secondly, recalls often occur years after a product goes on the market, since in the absence of clinical trials to provide warnings of risks or to gather scientific data after clearance, it can take many years to collect sufficient evidence to warrant a recall. Therefore, calculating the average number of 510(k) submissions from 2000 through 2009 is incorrect, because an unknown number of unsafe devices, especially those cleared most recently, have not been recalled yet.

For example, the FDA's high-risk recall of more than 70 million IV tubing sets and arterial catheters made by Arrow International included all lots dating from 2000 through 2009. The recall was not initiated until February 2010, almost 10 years after the devices were first sold. Similarly, prior to joining the FDA, Dr. William Maisel made a presentation to the Institute of Medicine stating that most of the recalls that occurred from 2003-2009 were for devices cleared by the FDA between 1996 and 2002. This delay between clearance and recall is not surprising, since the FDA does not require clinical trials before clearing a 510(k) device, making it difficult for physicians to know what adverse reactions are likely to be linked to the devices.

- **Just because a device has not been subject to a high-risk recall does not mean it is safe.** As noted above, high-risk recalls are based on evidence of harm that often takes years to gather and evaluate. Post-market studies are not required as a condition of approval for 510(k) devices, and therefore rarely conducted. The adverse reports submitted to the FDA are not automatically compiled by the FDA to determine the total number of adverse reactions to a specific device over the years.

The Battelle/AdvaMed report had different but equally serious methodological shortcomings compared to the Hall study. It did not make the mistake of using submissions; it more appropriately used the total number of devices **cleared** through the 510(k) process.

- However, the Battelle/AdvaMed **denominator included the total number of devices cleared since 1998 (at least 12 years), while calculating recalls only from January 2005 through May 2010 (5.5 years).** In other words, it did not subtract from the denominator the thousands of devices that were taken off the market for any reason, including but not limited to the estimated 10,000 high-, medium-, and low-risk recalls between 1998 and 2005.¹
- It also did not subtract from the denominator devices that were cleared between 1998 and 2009 but never sold in the U.S. Those devices should be subtracted from the denominator because they were previously recalled or not on the market during the study period of 2005 through May 2010.

Equally important, **all 3 studies analyzed high-risk recalls only.** Had the researchers analyzed all recalls, one would expect that the 510(k) devices would be much more likely to be recalled than the PMA devices, since there are so many more devices cleared through the 510(k) process. In contrast, high-risk recalls should have been rare for 510(k) devices, since they are defined as devices that “could cause serious health problems or death.”

Policy Recommendations

The 510(k) process has several major differences from the PMA process, all of which reduce safeguards for patients.

1. No clinical trials
2. No pre-market inspections
3. No post-market studies required as a condition of approval

The 510(k) process relies on bioengineering testing and other tests, rather than clinical trials. Although clinical data such as subjective reports are sometimes included, well-designed clinical trials are almost never part of the 510(k) criteria.

¹ According to the FDA web site, there were 1519 high, medium, and low risk recalls in 2005, and more than 1,200 each year in 2003 and 2004. The annual number of moderate-risk recalls (not including high or low risk) ranged from 1183 to 2007 from 2005 through 2009. The FDA web site does not include a list of moderate risk recalls for 1998-2002, but assuming similar statistics, we cautiously estimated 10,000 for 1998 through 2005.

If clinical trials were conducted, they would often catch errors of design or manufacturing before the product was sold. For example, if the accuracy of glucose test strips had been studied prior to approval, millions of patients would not have used inaccurate test strips and Abbott would not have had to recall more than 359 million test strips.

Even if a defective product were cleared for market without either clinical trials or pre-market inspections, requiring post-market studies as a condition of approval would allow problems to be caught more quickly than through non-scientific passive reporting of adverse events.

I recommend that, as the law requires, Class III devices always be subjected to the most rigorous review, the PMA process. In addition, devices subject to the PMA process should be defined to include all devices that can cause death when they fail. How can a low- or moderate-risk device create a predictable life-threatening situation? Glucose test strips used for diabetics are an excellent example: a seemingly simple product cleared through the 510(k) process. When Abbott glucose test strips were found to be very inaccurate in 2010, the FDA pointed out that when test strips falsely conclude that glucose is considerably higher or lower than it really is, the results can be fatal. That is why the FDA issued a high-risk recall of those strips in 2010, resulting in a recall of 359 million products.

Conclusions

American patients are dying and undergoing additional surgeries and hospitalizations that would have been avoided if their medical devices had been adequately studied or inspected before being allowed to be sold. Device problems would be caught much earlier if post-market surveillance was supported by adequate technological reporting systems, pre-market clinical trials, or post-market epidemiological research or clinical trials.

Medical devices are more ubiquitous than most people realize. Those of us who wear contact lenses or hearing aids, have an artificial hip or knee, had a LASIK procedure, have used Botox or other anti-wrinkle injections, or use glucose test strips to keep our diabetes under control, all rely on the safety and effectiveness of medical devices every day.

The importance of high-risk recalls does not depend on the total number of devices that are on the market compared to the small percentage that are recalled. The FDA approval process will never be perfect and so there will always be unsafe medical products, but small changes in the 510(k) process can make medical devices much safer. Lives could be saved and patients would spend less time in the hospital if FDA implemented the law as required by using the PMA process for all devices that are potentially dangerous in predictable ways. **Billions of Medicare dollars could be saved as well.** The 510(k) process, or a variation of it, may be acceptable for medical devices that are truly low- or moderate-risk, but not for implanted medical devices or devices used to diagnose or treat potentially deadly diseases.

My article in the *Archives of Internal Medicine* and the accompanying editorial are attached.

Hearing on the Safety of Medical Devices and FDA Oversight

Testimony of Frederic S. Resnic, MD MSc

Presented on April 13, 2011 to the Senate Subcommittee on Aging

Chairman Kohl, Senator Corker and the members of the subcommittee, I would like to thank you and your staffs for the privilege to present my perspective on challenges facing the effective monitoring of medical device safety in the United States.

The focus of my remarks today will be on:

1. Understanding the infrequent but very severe impact of medical device failures
2. Identifying existing barriers to effective post-market surveillance of medical device failures and safety risks.
3. Proposing a new paradigm, based on continuous automated surveillance to monitor clinical registries, to provide timely and meaningful information to regulators, the public and medical device manufacturers to substantially improve the safety of medical devices.

I am a practicing interventional cardiologist with Brigham and Women's Hospital and Harvard Medical School in Boston where I utilize many innovative and high risk medical devices in my daily medical practice. Complementing this practical experience, I have degrees in engineering and medical informatics, and I lead a research program funded by the National Institutes of Health and supported through research contracts by the FDA focused on strategies to monitor the safety of medical devices through continuous surveillance of health information registries and databases. I am here to present my opinions on how the U.S. could greatly improve the nation's medical device safety system to assure that patients are treated with technologies and approaches that are as safe as possible; recognizing that no device can be absolutely free of risk of failure. Please note that I am relaying my expert opinion and do not necessarily represent those of the medical center, medical school or the sponsors of my research.

To begin, I believe that the FDA Center for Devices and Radiologic Health (CDRH), and specifically their epidemiology and post-market surveillance divisions have made great progress over the past several years in addressing gaps in the safety net for medical devices. However, there is much yet to be done to adequately protect the public against infrequent, but potentially dangerous complications or failure of such devices. I also believe that the medical device manufacturer industry has recognized, over the past several years, the critical importance of comprehensive safety surveillance both for improving their products and also to reduce the significant business risk of any delay in recognizing and addressing a safety concern for one of their products. Given this alignment of interests, I believe there is a shared responsibility and a unique opportunity for the government including the FDA, device manufacturers, and scientific leaders in medical device safety surveillance to collaboratively examine and optimize the tools and strategies to assure the safety of patients receiving medical devices in the U.S.

The Hazards of Medical Device Failures and Safety Risks:

Key points:

1. Medical device safety failures are infrequent but often have severe consequences for affected patients.
2. Due to limited available usage information, there is often a significant time lag between the first reports of a medical device failure and when action is taken.
3. Within the last three years there have been numerous high risk medical device failures leading to injury and death of numerous U.S. patients.

The first issue to consider is risk of medical device failures that, while rare, can be devastating and represent a preventable public health risk in the United States. Within the past three years there have been several high profile medical device safety failures that have led to significant recalls, direct and indirect injuries for patients including additional procedures, and loss of life due to the failure of the device. Among the most recent have been the recall of the DePuy ASR XL Acetabular Hip System in August 2010 on the basis of an analysis of the National Joint Registry of England and Wales in which the DePuy hip suffered a 13% risk of requirement for hip revision within 5 years; far greater than the rates seen with other hip implants.

Unfortunately, this finding was not new. In fact, a high failure rate was noted in the Australian National Joint Replacement Registry and the manufacturer had voluntarily stopped selling the device in Australia in December 2009. It is estimated that thousands of U.S. patients underwent hip replacement with the DePuy system in the U.S. after the initial concerns were raised by the Australian study and before the formal recall was undertaken. As an aside, this particular product had been approved through the 510(k) pathway in 2003 and was not subject to specific clinical trial testing to confirm its safety or efficacy before market approval. [see Johnson and Johnson Website: <http://www.jnj.com/connect/news/all/deputy-orthopaedics-voluntarily-recalls-asr-hip-system>, accessed April 2, 2011]

A second recent device failure was the Medtronic Sprint Fidelis implantable defibrillator lead, which was recalled in October 2007. This device was recalled after release of the report indicating that the fracture of the lead may have been a contributing factor in the death of five patients. Again, this product had been approved for market release without any pre-market clinical testing to assure safety or efficacy. Medtronic had originally notified physicians in March 2007 of a limited number of reports regarding higher than expected Fidelis lead fracture rates, but on the basis of Medtronic's own analysis of a 100 patient registry, concluded that the Fidelis lead performed in-line with other ICD leads. However, even a cursory review would indicate that this post-market study was severely underpowered to detect any difference in lead fracture rates and should not have been used to reassure patients, providers or the FDA regarding lead fracture rates. Ultimately 268,000 Fidelis leads were sold and implanted world-wide, with a great number implanted in the U.S. [Maisei W. *N Engl J Med*; March 6, 2008]

Other notable medical device safety failures include the Guidant ICD battery failure (2005), the Cordis Cypher Drug Eluting stent (2005) and the Boston Scientific Taxus drug eluting stent (2004). Both of these stent recalls were, in fact, distinct from the overall controversy regarding overall risk of heart attacks with drug eluting stent (2006) which resulted in an emergent FDA public hearing on the safety of these devices. In each case the lack of a coherent clinical data registry made the identification of the existence, extent and severity of the problems much more difficult to estimate.

Key Challenges to Existing Medical Device Safety Surveillance:

Key points:

1. Current systems are passive and depend on voluntary reporting of adverse events
2. The GAO estimates that only 0.5% of all device adverse events are reported to FDA
3. Medical devices do not yet have a unique identifier in administrative or claims data complicating efforts to systematically study their use and safety
4. Other challenges such as learning curve effects, and rapid product lifecycle are unique to medical devices and will challenge current plans such as the FDA Sentinel Initiative.

The systems currently used to assure that medical devices are safe are primarily a patchwork of voluntary and passive event reporting mechanisms administered through the FDA. These systems, including MAUDE, MDR and MedSun principally rely upon incident reports to the FDA, which then sifts through these reports to look for clusters or trends. With more than 125,000 incident reports submitted per year by hospitals, physicians and manufacturers, these systems provide a great deal of critically important information to the FDA regarding the safety of devices, and are invaluable for gathering detailed information regarding the circumstances leading to rare or unexpected events. Despite significant efforts by FDA to encourage comprehensive reporting of medical device complications and failures, the actual proportion of experienced medical device failures is very low. In fact, the GAO has estimated that less than 0.5% of actual device failures or complications are reported, thus tremendously limiting the information available to make judgments regarding the relative balance of safety risk and health improvement that a medical device might provide to patients. [*Gross TP, Kessler LG. Stud Health Technol Inform 1996;128:17-24*] In addition, this passive reporting system provides information only about the problems reported, but does not give any information regarding the usage of the device; the “denominator” information, so that the rate of a specific device failing can be compared with other similar devices or some benchmark for acceptable performance. It is also critical to note that the approval of medical devices, even through the most rigorous pre-market randomized trial, can not effectively address the very low frequency safety risks that may be experienced only once the device is available for use in much larger “real-world” patient populations that occurs in the post-approval timeframe.

In 2008 the FDA launched a major effort to connect large healthcare dataset owners throughout the country as part of a “Sentinel” initiative, in order to have timely access to post-approval data for approved medical products. [*Platt R, Wilson M, Chan KA, Benner JS, Marchibroda J and McClellan M. N Engl J Med; 361(7) August 2009*]. However, the unique requirements of medical device safety surveillance will clearly challenge the current planned structure of the Sentinel program. In fact, despite several years of planning and evolution, the Sentinel program has yet to address medical device safety at all.

Among the challenges specific to medical devices which greatly complicate post-market surveillance, include the absence of unique device identifier information for the monitoring of medical device safety. In contrast to medications, the absence of a unique device identifier (UDI) severely limits the utility of existing healthcare administrative claims datasets, which form the core of routinely collected data used by the Sentinel network. Secondly, most complex and high risk medical devices are refined and improved through a rapid product lifecycle,

making it essential to have extremely timely analysis and interpretation of any potential safety signals before a device is replaced by a next generation product. Also, unlike medications there is a complex interplay between the experience of the surgeon or proceduralist implanting or using a high risk medical device and the potential harm the device might cause, through effects such as “learning curves” and team or healthcare center training levels. Finally, for novel medical devices, there may be few alternatives against which to compare in terms of adverse events, making assessments of relative safety very challenging. All of these attributes of medical devices will challenge the current strategies for connecting existing healthcare clinical and administrative datasets to provide meaningful, timely and effective medical device safety surveillance.

A Better Approach – Automated Continuous Safety Surveillance:

Key points:

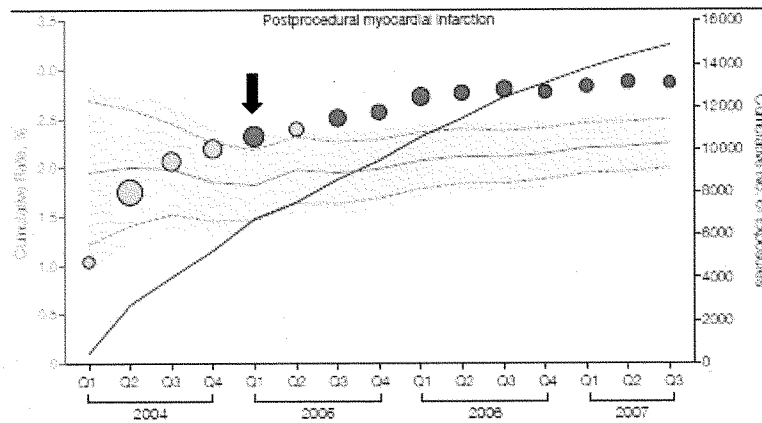
1. Recent studies have demonstrated that automated surveillance tools can effectively detect low frequency safety signals not discovered through other means.
2. Such approaches can greatly reduce the time to discover safety risks thereby sparing additional patients the exposure to the device.
3. Best available methods to maximize detection of true safety signals while minimizing risk of “false alarms” can be incorporated in such automated surveillance tools.

Despite these challenges to monitoring device safety, I believe there is a path to achieve an organized, coordinated and rational approach to post-market medical device safety surveillance that would not stifle innovation nor delay the release of important healthcare advances to the public. This strategy would be based on the use of available and emerging computerized tools to support continuous surveillance of health information registries to detect unexpected safety signals in a timely manner. I believe such a strategy could be sustainably funded through the use of existing fees assessed during the medical device approval process without incurring additional costs to the medical device manufacturer industry. Specifically, I believe that the use of continuous monitoring tools, constantly looking for evidence of safety signals for high risk medical devices is an immediately feasible strategy that would dramatically improve the current voluntary or passive approach of medical device post-market safety assurance. These monitoring tools already exist, and incorporate the best available statistical methods to account for some of the complexity of medical device safety surveillance, such as the differences in risk between patients, learning curves or interactions of the device with other medical conditions or medications used.

In research recently published by my group in the Journal of the American Medical Association, we developed and tested a computerized safety surveillance system and applied this tool to a statewide registry of cardiac procedures in MA. Our study monitored the adverse events of more than 74,000 heart stent procedures performed between 2005 and 2007 and identified two out of seven medical devices which experienced 20% to 50% higher rates of heart attacks or major bleeding following the procedure as compared with similar products in matched patient groups. In Figure 1, below, the accrual of matched patients from the registry allows us to compare, head to head, one device against identical patients receiving an alternative device. Within 18 months of the start of this monitoring, we detected the significantly increased rates of

heart attacks for one type of drug eluting stent as indicated by the red plotted points. This exploration was the first such study to demonstrate the feasibility of applying continuous surveillance to a detailed medical device specific registry. [Resnic FS, Gross TP, Marinac-Dabic D et al. *JAMA*; 304(18): November 2010 – included as Appendix I]

Figure 1: Risk of Heart Attack following treatment with Taxus Drug Eluting Stent (DES): The graph plots the propensity matched analysis of the cumulative incidence of heart attacks following implantation of at least one Taxus DES. Circles indicate the cumulative observed event rates for patients receiving Taxus DES. The dark arrow indicate the point at which the automated system detected a significantly higher rate of heart attacks for the Taxus stent as compared with other DES. Please see Appendix 1 for full description of analysis.

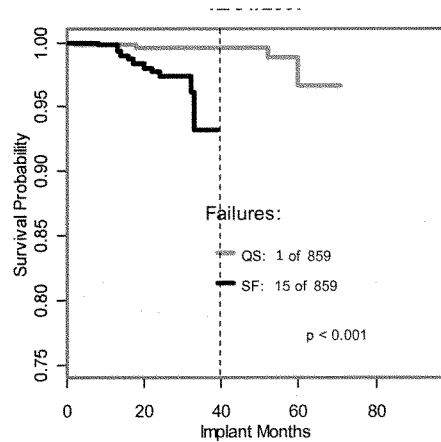


In response to this research, international experts in healthcare safety and quality including Dr. John Rumsfeld, Acting National Director of Cardiology for the Veterans Administration Healthcare System, and Dr. Eric Peterson Associate Director of the Duke Clinical Research Institute have called for broadly applying the approach of using automated surveillance to medical outcomes registries as a principle way to improve the safety surveillance of medical devices in the United States. [Rumsfeld JS and Peterson ED. *JAMA* 304(18): November 2010]

In a separate study, Dr. Robert Hauser, a leading advocate for cardiovascular device safety used the same computerized surveillance system to show how quickly automated surveillance could have identified the increased risks of the Fidelis implantable defibrillator lead fracture, had the system been monitoring the accruing data at just four academic medical centers. In this study, the system was able to identify Fidelis lead fractures 14 months before the traditional methods of analysis were able to show a difference. This time savings, if acted upon promptly by FDA, could have spared thousands people from having these systems implanted. Importantly, this

early warning would have also spared the manufacturer, Medtronic, from having a relatively small problem snowball into an enormously complex safety issue.

Figure 2: Monthly prospective propensity matched survival analysis comparing Sprint Fidelis to control implantable cardio-defibrillator leads. The durability of each lead type is plotted against the months following implant. By 40 months of analysis (dashed line) 1.7% (15 of 859) of Fidelis leads had fractured (black line) whereas only 0.1% (1 of 859) alternative ICD leads had fractured; representing a more than 10 fold device failure rate.



Importantly, the automated surveillance system tested in the studies above incorporate a variety of statistical approaches to maximize the detection of safety signals, while attempting to minimize the number of “false alarms” generated by the system. Systems such as this also are capable of monitoring hundreds simultaneous medical devices, so as to maximize the efficiency of using such systems. Additional explorations are currently underway linking a network of orthopedic implant databases as well as within the VAHS clinical data repositories, and should provide further information on the opportunities as well as limitations of automated surveillance approaches to medical device safety signal detection.

The Critical Need for National Medical Device Registries

Key points:

1. Detailed clinical registries provide the necessary granular clinical information needed to support automated safety surveillance.
2. There is no current process or regulation to assure that all high risk devices are followed in detailed clinical registries.
3. The best such registries in the U.S. are currently initiated, funded and maintained by non-profit professional medical societies or large healthcare provider systems.
4. Aligning resources and incentives in a public-private partnership, such as the INTERMACS registry of cardiac support devices may serve as a template for future medical device registries

Of course, having reliable tools able compare the relative performance and safety of medical devices marketed in the United States is a critical component for improving the safety net for medical devices, but is not enough to improve safety without reliable datasets to monitor. We must have accurate, reliable, and increasing bodies of information in useful and accessible datasets on which to base this model of continuous safety surveillance. Fortunately, voluntary detailed clinical registries capable of providing the necessarily detailed clinical information already exist in the selected medical fields, covering hundreds of high risk devices. In many countries, such registries are a mandatory component of the healthcare system and required for all high risk implant procedures. Examples of such registries include the Australian and UK joint replacement registries, from which the risks associated with the DePuy implant were discovered.

In the U.S. however, such registries have been developed primarily through non-profit professional organizations originally intended to analyze and improve the quality of care delivered, and not specifically for medical device surveillance. The American College of Cardiology, in conjunction with several partner professional organizations, have established leading detailed clinical datasets as part of their National Cardiovascular Data Repositories (NCDR), covering the fields of interventional cardiology (coronary stents, angioplasty balloons, vascular closure devices), a registry for ICD's, a registry for carotid stents, and will soon be launching several registries covering additional cardiovascular fields and their associated devices. The largest of these registries, CathPCI, includes over 3.1 million patient level records with device level information from over 1,100 participating facilities in the United States. In addition to the American College of Cardiology programs, the Society of Thoracic Surgery has a comprehensive clinical registry with detailed information on cardiac surgical implants. New efforts by professional societies within orthopedics, ophthalmology, and surgical material implants are also underway.

Creating and maintaining these detailed clinical registries is challenging and expensive. Today many of our registries are supported by voluntary submissions from health providers requiring hospitals to bear all of the costs of collecting and submitting the case level information. However, emerging standards for electronic health records including the "meaningful use" regulations being implemented over the next several years will provide unprecedented opportunities for securely mapping clinical information to distributed clinical registries. This

health care information revolution will dramatically increase the ability to extract the necessary information, and should greatly reduce the cost of collecting detailed medical device safety information to permit surveillance from hospital-based and clinical practice based health information systems.

Perhaps the most innovative example of bringing multiple stakeholders together into a coordinated effort to study newly introduced medical devices has been the INTERMACS registry, a public private partnership involving the National Institutes of Health, Center for Medicare Services, FDA, industry representatives and academia. The INTERMACS registry was established in 2006 to capture the clinical data and outcomes of all patients receiving mechanical heart support pumps in the U.S. Importantly, CMS created the incentive for participation in INTERMACS by requiring that every patient's information be entered into an audited national registry as a condition for reimbursement for the procedure. INTERMACS has provided a model for the collection, timely analysis and dissemination of information that improves care for these complex patients. Since its inception, INTERMACS has provided tremendous information on the safety and effectiveness of mechanical heart support therapies on groups of patients who were not studied in the initial randomized pre-approval trials, enabling rapid dissemination of knowledge and moving the care of these patients forward at a rapid pace. Importantly, INTERMACS also serves as a ready infrastructure to support the post-approval study of every new generation of mechanical cardiac support device since the initiation of the registry, saving the manufacturers significantly by avoiding the requirement to establish redundant systems of data collection, auditing and analysis. [Miller MA, Ullisney K and Baldwin JT. *J. Am Coll Cardiol* 2010;56(9):738-740].

The INTERMACS experience provides a template that could form the basis for future prospective surveillance for all high risk medical devices, in that it aligned the incentives of healthcare providers with the needs of the public health and public policy organizations to collect, analyze and disseminate device level analyses using detailed clinical registry information for all patients receiving a new device. Looking ahead, developing similar public-private partnerships to collect detailed clinical information in the form of clinical registries, and coupling these data sources with the tools for automated prospective surveillance, as described above, will provide the best mechanism to minimize the health risk of new medical devices.

Also notable in the push toward more comprehensive medical device active surveillance, relying on such detailed clinical registries, is the leadership of the FDA CDRH in bringing together dataset owners to participate in critically important collaborative device safety pilot projects. A recently launched initiative within CDRH, called the Medical Device Epidemiology Network or MDEpiNet focuses on developing the best methods to study these types of emerging data resources, and seeks to establish a variety of public-private partnerships to make the greatest use of these device specific registries.

Summary and Specific Recommendations:

In summary, the post-approval monitoring of medical devices in the United States requires significant enhancement to avoid preventable injury and death to patients treated with high risk medical devices that ultimately fail. Current passive event reporting systems are inadequate to provide the critical information to regulators, public health officials, physicians and patients as to the relative safety and performance of new medical devices. Unique and specific challenges for studying medical devices, such as the lack of unique device identifiers, intrinsic learning curve effects, and interactions between devices, medications and medical conditions may challenge current advanced monitoring strategies such as the Sentinel initiative. Pilot studies have demonstrated that advanced automated safety surveillance tools can simultaneously monitor numerous medical devices for multiple safety outcomes to identify low frequency safety signals. Such systems could prevent exposure of patients to devices which would put them at uniquely increased risk. In order to facilitate such a broad surveillance network, regulators and industry must look to well organized clinical registries with sufficient detail to support post-market surveillance of specific high risk medical devices.

In order to achieve the goals outlined above, I would respectfully ask the committee to consider the following recommendations:

1. FDA, in collaboration with CMS, should mandate that detailed information regarding high risk medical device use and clinical outcomes be universally submitted to selected national clinical registries.
2. The registries should be operated by independent academic or professional society organizations as part of public-private partnerships, informed and guided by MDEpiNet and the Sentinel Initiative and other federal stakeholders.
3. FDA should redirect resources currently spent by the medical device industry on condition of approval studies to support the national medical device safety registries.
4. Automated safety surveillance tools should be uniformly applied to the device registries to continuously and prospectively monitor each registry for the most severe as well as most common complications and failures of each high risk medical device.
5. The results of the automated surveillance should be provided, in real time, to both the FDA, to complement existing event reporting systems, as well as to manufacturers to support refinements in product design.

Thank you again for the opportunity to share my thoughts on this very important topic with this committee.

Written Statement

Ralph F. Hall

Distinguished Professor and Practitioner

University of Minnesota Law School

U.S. Senate Committee on Aging

A Delicate Balance: FDA and the Reform of the Medical Device Approval Process

April 13, 2011

Good afternoon, my name is Ralph F. Hall. I appreciate this opportunity to speak to this committee on these important medical device matters affecting patients, physicians, innovation and jobs. I am here to discuss research I have done into the safety of 510(k) products and to discuss CDRH's post-market authorities and its recall authority and practices. I am here speaking in my personal capacity and not on behalf of the University of Minnesota or any other entity.

Background and Disclosures

To start, I serve as Distinguished Professor and Practitioner at the University of Minnesota Law School where I concentrate my teaching, research and writing in the area of FDA law and compliance matters. In addition, I am part time Counsel at the law firm of Baker & Daniels where I work with clients on a variety of FDA matters and also provide counsel to a national 510(k) coalition. Finally, I serve as CEO at MR3 Medical LLC. – a four person start-up medical device company working on a new technology for cardiac rhythm devices generally regulated under the PMA process.

The research that is the focus of many of my comments was funded by the Ewing Marion Kauffman Foundation, a private nonpartisan foundation based in Kansas City, MO. Their generous support made this research possible. The Kauffman Foundation has given me complete academic freedom to pursue this research.¹

Study Summary

The safety of medical devices is, of course, of prime importance to patients, physicians and other stakeholders. Rather than look at isolated or individual events, opinion or anecdote, I am interested in the performance of the system as a whole. It is critical to remember that all devices carry with them some risk. While all stakeholders strive for devices with no post-marketing safety questions, such perfection is impossible.

The study I focus my comments on assesses the overall safety profile of medical devices approved or cleared by FDA from 2005-2009 by using Class I safety recall data. This study² evaluated Class I (or high risk) recalls of all medical devices, regardless of whether they were approved through the PMA system, cleared through the 510(k) process or were otherwise exempt.

The key conclusions from my research are as follows:

1. Overall, 510(k) regulated medical devices have an excellent safety profile. Over 99.5% of 510(k) submissions assessed during this study period did not result in a Class I safety

¹ I want to thank Amanda Maccoux, Mark Jones, Chris Walker and Ron Song - the research assistants at the University of Minnesota Law School who spent long hours doing the detailed data collection and coding required for this study. Their talents, hard work and dedication are vital to this research and I appreciate all that they did.

² An earlier version of this research into the safety of medicals devices through an analysis of safety recalls was presented to the Institute of Medicine committee reviewing the 510(k) system, reviewed with FDA and is being prepared for submission to a major peer reviewed journal.

recall. Over 99.7% of 510(k) submissions did not result in a Class I recall for any reason relevant to the 510(k) premarket system.

2. Products approved through the PMA system also have an excellent safety record. Again, greater than 99.5% of PMA or sPMA submissions do not result in a Class I safety recall during the study period.
3. Very few (less than 9%), Class I recalls during the study period involve possible undiscovered clinical risks. As such, increased preapproval clinical testing would not have any meaningful impact on reducing the number of Class I recalls.
4. The majority (approximately 55%) of all Class I recalls involve problems or issues that arose after market release and could not be affected by premarket approval systems or requirements. For example, a manufacturing mistake made three years after FDA approval or clearance may trigger a Class I recall. However, any premarket requirements such as clinical testing are irrelevant to preventing such a recall.
5. A very significant majority (over 90%) of all Class I recalls (including both premarket and post-market issues) are directly related to quality system issues (so-called QSR systems³). Improved QSR systems will have the greatest effect in reducing the number of Class I recalls.
6. My study did identify a bolus of Class I recalls in two device types – automatic external defibrillators (AEDs) and infusion pumps. Any changes to the premarket review process

³ QSR requirements are intended to provide “cradle to grave” product quality in a closed loop, learning system. QSRs include design input and processes, design validation, product testing, manufacturing controls, process controls, change controls, management review and post-market assessments. See, generally, 21 C.F.R. § 820.

should be targeted to demonstrate problems rather than applied in some random, shotgun way.

7. Finally, one should not confuse classification for premarket review processes with recall classification. These are very different things and serve very different purposes.

Study Background

The need for the research that I will describe goes back several years when a number of stakeholders started to question the robustness of the 510(k) system. I was and am familiar with the numerous issues relating to delays in submission reviews and changing data requirements. I was, however, struck by the belief among some that the 510(k) system did not assess or consider product safety in making clearance decisions and that there was some major issue with the safety of products being cleared by the 510(k). First, it is critical to note that FDA does consider safety when deciding whether to clear a 510(k) submission. A number of commentators seemed to not be aware of this. Second, some stakeholders were advocating making major changes in the 510(k) system to address presumed safety problems. I was particularly struck by the fact that there was no good, objective data to support or refute the assertion that the 510(k) system needed to be changed because of these presumed safety issues.

In fact, at an early public meeting held by FDA to discuss making major changes to the 510(k) system, I commented that this was a “ready, fire, aim” exercise in which various interest groups were advocating major changes without any understanding of the actual performance of the system and any issues with the system. It struck me then and now that data, not opinion, should drive policy changes.

Some commentators then and now simply looked at the number of 510(k) recalls compared to PMA recalls. While not directly comparable, one must remember that there are around 3,500 510(k) submissions per year compared to 20-40 PMA applications (and some additional number of sPMA submissions). Given these disparate numbers, the fact that more recalls are for 510(k) products than PMA products is not meaningful or even a useful comparison. A more systematic study was needed.

Given my concerns over the lack of hard data, I commenced a study (with the able assistance of four research assistants) assessing the safety performance of FDA approval processes. To my knowledge, this was the first study designed to systemically assess the safety performance of the 510(k) system. This study was funded by the private, nonpartisan Kauffman Foundation. I am solely responsible for the study and its results.

Study Methodology

This study assessed the overall safety profile of medical devices approved or cleared by FDA from 2005-2009 by using Class I safety recall data.

Class I safety recalls were chosen as the measure of safety as these recalls involve any medical device problem posing any significant risk of serious health consequences to patients and also correctly exclude risks considered as part of the approval or review process. Class II recalls involve generally remote risks to patients and Class III recalls involve minimal or no risk to patients. FDA, not industry, is responsible for assigning the recall classification. Note that the Class of recall assigned by FDA is independent of the product's device classification. For example, no one would argue that a tongue depressor is a high-risk device or needs a clinical trial. For premarket purposes it is classified as a low-risk, exempt device. However, if the

tongue depressor gets contaminated with deadly bacteria because of product tampering or some manufacturing problem there is a significant risk to patients. This would be a high-risk or Class I recall even though for premarket review purposes it is a low risk device.

Using FDA databases, we identified all Class I recalls posted by FDA on public databases during 2005-2009. We first combined all duplicate recalls into one data set of unique or stand alone recalls. (FDA may have several recall announcements and thus there may be multiple data entries for the same issue because of different package configurations, brand names or product sizes).

One hundred eighteen (118) unique recalls were identified. We then coded each recall for a number of factors including regulatory pathway, medical specialty, whether implantable and three letter product code. We also coded each recall with one of thirteen reasons for recalls. Generally speaking, these thirteen recall reasons can be combined into three broad groupings of premarket issues (*i.e.*, something that could, at least theoretically, have been discovered during a premarket review process), post-market issues and miscellaneous (counterfeit and “quack” products). We used FDA websites and publicly available information for this coding.

All data was entered into a standard Excel spreadsheet following quality control.

This study must be assessed in light of the following factors:

1. First, we relied entirely upon publicly available data. We assume that the information in the FDA databases is correct. We did not identify any meaningful errors in this data but did not conduct any structured assessment of the accuracy of FDA’s data.

2. Second, while companies are obligated to report recalls, there may be situations in which the company failed to meet this obligation. We believe that any such missing recalls would tend to be small and not common because of the penalties for non-compliance and the variety of information sources that would disclose any such recall. Importantly, there is no reason to believe that the distribution of the causes of such recalls would be different than the data we had.
3. Third, we reviewed Class I recalls and not Class II recalls. (FDA defines a Class II recall as a situation in which the problem “might cause a temporary health problem, or pose only a slight threat of a serious nature.) We believe that Class I recalls represent all recalls with any meaningful risk to patients and so represent a valid safety picture. Remember that Class II recalls are for remote risks or low impact problems. Class I recalls represent the majority of actual patient risk and tend to err in the direction of higher rather than lower classification. Risks as low as 1/20,000 have been classified as Class I recalls thus demonstrating the breadth of risks captured by Class I recalls.
4. Anecdotal review of some Class II recalls indicate (but do not establish) the same general pattern of reasons for recalls between Class I and Class II recalls.
5. Finally we did not assess any effects of various regulatory systems or actions on patient access to new products, innovation or the economy in general.

In designing this study, we considered other methodologies; including reviewing adverse event reports (generally referred to as Medical Device Reports or MDR reports) and also tried to assess number of products involved in each recall. In these cases, the data is hopelessly inaccurate and

incomplete, inaccurately counts actual events as compared to the risk of a malfunction or is not related to the binary decision to approve or not approve the submission.

We also determined the percentage of 510(k) submissions that resulted in a subsequent Class I recall. The numerator for this calculation is the number of recalls. The denominator is the number of submissions. The denominator for this calculation is a close estimate as there is no direct connection between the date of the submission and the subsequent recall. For example, a recall for a design defect might occur within a month after market release while a recall for a manufacturing error or packaging mistake could occur literally years after approval or clearance.

We determined an annualized number of submissions by taking the average number of submissions for a ten-year period (2000-2009) and annualizing that number. We used this number for all percentage calculations. Those percentages, however, are approximations due to this data challenge.

Study Results and Data

Initially, we looked at the reasons for recalls for these 118 Class I recalls. It must be remembered that all devices carry risk and that Congress has balanced patient access to new technology with premarket processes by creating the standard that there must be "reasonable assurance" of product safety before the product should be marketed. We determined the reason for the recall by examining FDA's public databases and also reviewing publically available information including physician notification letters and SEC filings. I was responsible for all decisions relating to the reason for recall. I blindly recoded 10% of the recalls and had a complete match with the initial determination of the reason for the recall.

The following table shows the number of recalls by regulatory pathway and the reason for recall.

Reasons for recall in blue are those related, at least potentially, to premarket review processes.

The others are recall reasons that are completely unrelated to any premarket process.

Primary Reason for Recall	PMA	510K	Class 1	Other or Unknown	TOTAL
Manufacturing	6	31	2	1	40
Labeling Error	0	4	0	0	4
Design Issue	6	25	1	0	32
Software Design	1	9	0	0	10
Software Manuf. Failure	0	2	0	0	2
Supplier Issue	2	5	0	0	7
Failure to Identify Clinical Risk	0	0	0	0	0
Failure to Warn/Inadequate Instructions	0	8	0	0	8
Missing Parts	0	0	0	0	0
Sterilization	1	4	2	0	7
Regulatory Violation	0	1	1	0	2
Packaging/Handling	0	0	0	0	0
Other (Counterfeit, Sham)	0	6	0	0	6

As shown below, the majority of all recalls (approximately 55%) are for post-market issues. For

these recalls, no change in the premarket 510(k) or PMA process would affect the recall

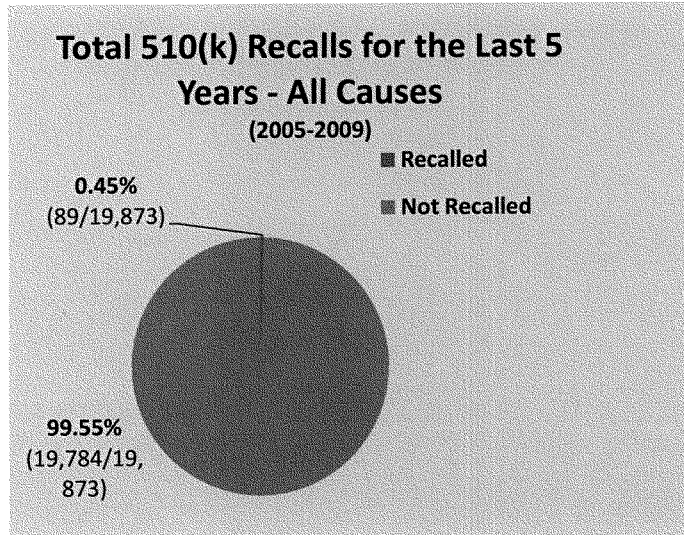
occurrence or frequency.

	Total Recalls	Recalls for Pre-Market Issues	Recalled for Post-Market Issues	Recalled for Other Issues	Percent of Recalls to Total Recalls
Class I or u/k	7	1 (14.2%)	6 (85.7%)	0 (0%)	5.9%
510(k)	95	43 (45.3%)	46 (48.4%)	6 (6.3%)	80.5%
PMA	16	7 (43.8%)	9 (56.3%)	0 (0%)	13.56%
TOTAL	118	51	61	6	118

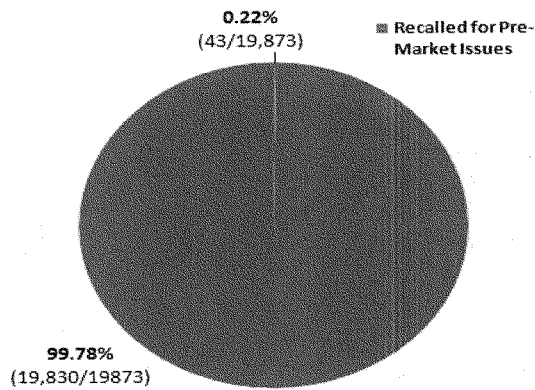
As seen below, a very small percentage of 510(k) submissions led to a Class I recall during our study period. The first chart shows the ratio of 510(k) submissions to all Class I recalls and the second chart shows the ratio of 510(k) submissions to Class I recalls related to any theoretical premarket issue.

This data shows that CDRH and the submission sponsors have done an admirable job in identifying potential device risks, particularly clinical risks, prior to the approval or clearance decision. These risks can then be explicitly balanced against benefits as part of that premarket decision. Very few, if any, recalls in the device world are related to undiscovered clinical issues.

Based on this data, approximately 99.55% of all 510(k) submissions did not result in a Class I recall for any issue during the study period. More importantly for assessing the 510(k) process, approximately 99.78% of all 510(k) submissions did not result in a Class I recall for any reason related to the premarket process. Stated differently, the maximum theoretical impact of any change in the 510(k) system would be on 0.22% of all 510(k) submissions. This data also demonstrates that additional premarket clinical testing would be ineffective in reducing Class I safety recalls.



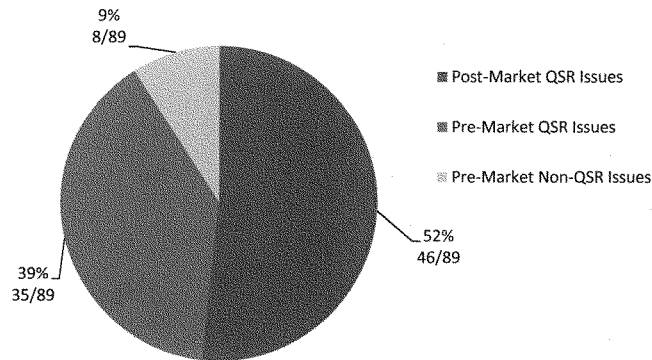
Total 510(k) Recalls for the Last 5 years – Pre-market issues



Total 510(k) Submissions in 10 years	39,747
Average Submissions in 5 year time period	19,873
Total 510(k) Recalls for 2005-2009	89
Total 510(k) Recalls for Pre-Market Issues for 2005-2009	43

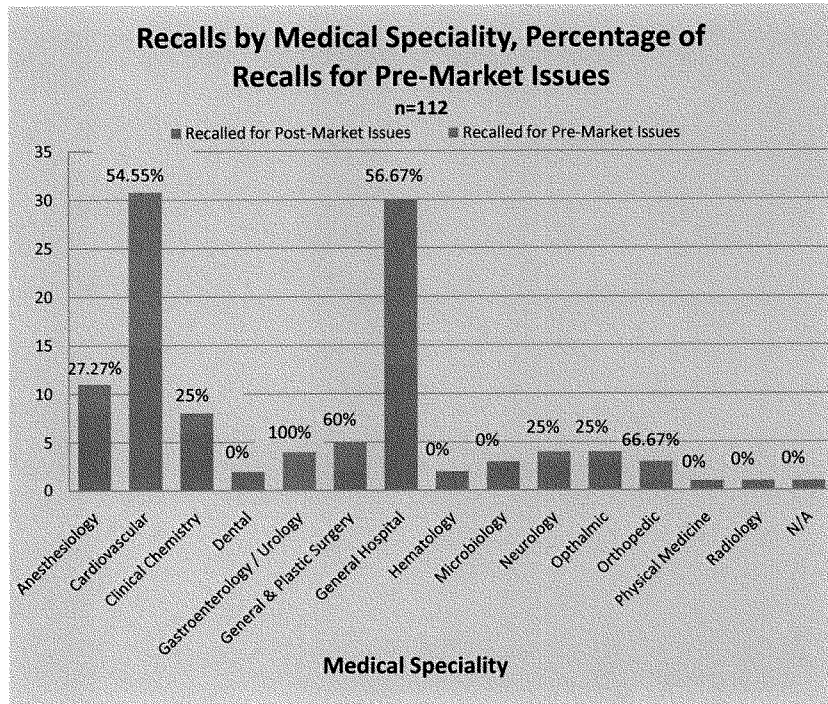
The number of recalls related to premarket issues is most relevant in assessing whether the 510(k) system is adequately addressing patient safety during the review process. This data demonstrates that post-market issues, not premarket processes, should be the focus to improve patient safety.

This conclusion is reinforced when we reviewed the role of quality systems in recalls. As shown below, over 90% of all Class I safety recalls are related to quality system issues and not to other factors such as a lack of clinical trials.



Clearly, this data demonstrates that all stakeholders should concentrate on QSR systems such as design control and bench testing — not the 510(k) submission system — as the most effective way to provide greater patient safety.

We also did sub-analysis by product type and medical specialty. Such analysis can be used to identify concentrations of issues for further investigation by FDA, industry and other stakeholders. As seen below, Class I recalls are concentrated in several product types.



Further analysis indicated that automatic external defibrillators (AEDs) and infusion pumps accounted for 28% of all Class I recalls and accounted for a substantial part of the bolus or recalls seen in the cardiovascular and general hospital categories. Within the past nine months, FDA has triggered new regulatory initiatives for both AEDs and infusion pumps.

This data also shows remarkably few Class I recalls for a number of product areas, including some product types that have been recently agued demonstrating flaws with the 510(k) system, such as orthopedics, radiology and OB/GYN.

We also assessed the data to see whether implantable products or submissions that went through the third party review process had any concentration of Class I recalls. Our analysis showed that Class I recalls for implantable devices almost exactly matched the expected percentage of recalls and that there were fewer recalls for submissions reviewed under the 510(k) third party review system than might be expected.

Our confidence in our study design and results has been bolstered by subsequent studies by others such as FDA itself, Dr. Maisel and Battelle finding very similar numbers and reasons for Class I recalls.

We have also obtained some internal FDA information on recalls via FOIA. While we do not have complete information and our analysis is very much in a preliminary stage, this in process assessment is also consistent with the analysis reported above. In fact, preliminary analysis indicates that FDA believes that more recalls are for post-market reasons than our analysis (based on public documents) indicates. FDA's public statements also support our analysis indicating that the majority of product recalls are caused by post-market issues.

Study Conclusion

This study demonstrates that very few 510(k) medical device submissions — less than 0.5% — become the subject of a Class I safety recall. Even in this small number of Class I recalls, the majority of Class I recalls involve post-market issues such as manufacturing mistakes, and are focused around two product categories (cardiovascular and general hospital). These recalls involve quality system issues, not premarket issues. Overall, in excess of 90% of all recalls appear to involve quality system issues.

Our study shows that FDA has a very positive safety record in its 510(k) clearance decisions.

Post-Market Authorities

In assessing post-market issues, it is absolutely critical to differentiate between CDRH's statutory authorities and the use or implementation of the authority which they possess. Gaps in statutory authority, if any, may well need to be addressed via legislation. Conversely, Congressional or stakeholder concerns with CDRH's use or implementation of such authority should not be addressed through legislative changes. Rather, such issues should be addressed by other means, depending upon the specific issues, such as budget changes, changes in resource allocations, changes in priorities, management modifications, etc.

CDRH has extensive post-market authority under the current statutory system. These authorities can be categorized as either general (or universal) requirements or device product type of situation specific. The first group is applicable to all devices; the second are applicable to defined subgroups.

Universal Post-Market Requirements

The following legal/regulatory structures generally apply to all medical devices.

1. MDR Reporting

Pursuant to 21 C.F.R. § 803 (and related authorizing statutes such as 21 U.S.C. § 360i(a) and (b)), medical device manufacturers are required to submit any reports of deaths or serious injuries allegedly associated with the device or device malfunctions which could, if such a malfunction were to occur in the future, cause death or serious injury. Failure to submit MDR reports can (and often do) lead to serious enforcement actions.

It is important to note that the regulatory definition of “serious injury” includes a wide variety of events including events in which medical intervention prevented an actual serious injury. For example, a product issue that extended the time of the operation by ten minutes would be “serious injury” under 21 C.F.R. § 803 even if there was no other patient impact. Stated differently, the regulatory definition of “serious injury” is much broader than what the lay person or physician might consider serious.

It is also critical to note that MDRs are to be submitted within specified time frames even if the allegations are unproven or open to debate. Causation need not be established and an investigation need not be completed before the MDR must be submitted. Approximately 180-200,000 MDRs are reported each year.

Properly implemented, the MDR system provides an ongoing assessment of product performance in real world situations and operates as an “early warning system” for unknown safety issues or changes in the frequency or severity of known risks.

2. Recall Reporting

Under 21 C.F.R. § 806 (and related statutes and guidance), companies are obligated to report to FDA within ten days any field action (technically, either a correction or removal action) related to product issues or regulatory matters. These reports and subsequent recall effectiveness checks and recall close outs provide FDA with information about field performance issues and permit the agency to learn about field issues and address (with that company or others with similar products), field performance issues.

3. MedSun

The MDR system is a “passive” data collection system. To complement this “passive” system, CDRH has implemented (and is currently upgrading) the MedSun program. The program actively collects product performance data from approximately 350 hospitals covering different geographies and types of patient base (urban and rural, small and large, academic teaching centers and non-academic centers, etc). CDRH has special relations with these institutions and has trained these institutions to actively report product issues.

The Medsun system provides enhances field surveillance and the collection of more data in a structured, organized fashion.

4. QSR Systems

A critical element of CDRH's post-market safety and surveillance systems are the Quality System Regulations (or QSRs) generally set forth in 21 C.F.R. § 820. These require each company to collect and analyze all product complaints. These must be investigated to determine root cause and appropriate reporting (often MDR filings) must take place. The company has an obligation to look not just at events in isolation but to trend events and look for commonality of issues across product lines.

Properly implemented, these QSR processes (and related manufacturing and product development and testing), are robust tools to identify and analyze product performance.

5. Inspections

FDA has the authority to inspect any medical device manufacturer. These inspections routinely cover QSR systems, compliant files, complaint investigations, root cause analysis, event trending, product modifications and recall activity. Inspectors have access to all relevant documentation and to individuals responsible for these various activities. Such inspections can be either "routine" or "for cause" if FDA suspects or has knowledge of some product performance issue. A failure or refusal to supply relevant information or documents or supplying false information can be a criminal offense.

6. Product Tracking

Post-market surveillance (and recalls as discussed below) is enhanced as one can link products to events and identify specific products. This is no small challenge given the literally billions of devices on the market that are used in a wide variety of settings outside the knowledge or control of the manufacturer by users or consumers over which FDA has little if any regulatory authority. In addition, multiple devices are used in a single therapeutic setting and are often serving an ancillary role to the more obvious therapy delivery. There may be literally hundreds of devices used in a cardiac surgical procedure.

FDA's unique device identification (UDI) program should significantly improve the agency's ability to track devices and link specific devices to events. In addition, FDA can, for implantable and high risk devices, impose specific device tracking requirements under 21 U.S.C. § 360i(e) (FDCA § 519(e)).

7. Reports of Product Modifications or Changes

Under both the PMA and 510K systems, companies are also obligated to report to CDRH product modifications made to address field issues. This process provides CDRH another view into product performance and can trigger inquiries about related products or systems. Product modifications that must be reported include physical changes to the device and also changes in the labeling such as new warnings or instructions for use.

Specific Post-market Systems or Obligations

For certain products, more tailored or specific post-market surveillance may be appropriate. These are in addition to, not in lieu of, the general or universal post-market obligations described above. CDRH has a wide variety of statutory authorities by which it can impose such tailored post-market surveillance obligations.

1. Conditions of Approval

PMA product approvals include mandatory “conditions of approval” (see 21 C.F.R. § 814.82(a)(2)). These vary between product types but can include enhanced post-market surveillance, post-market testing, increased reporting, patient registries, etc. These post-market obligations can be tailored to the particular needs of the patients and products themselves thus allowing for more focused and relevant post-market surveillance.

2. Special Controls

In an analogous way, Class II products can be subjected to special controls under 21 U.S.C. § 360c(a)(1)(B) (FDCA § 513(a)(1)(B)). These special controls can require any number of post-market obligations including patient registries, dissemination of product use guidelines, post-market surveillance plans, etc. In addition to these specifically enumerated tools, the FDA can mandate “other appropriate actions as the Secretary deems necessary to provide such assurance [of safety and efficacy].”

3. Section 522 Orders

In 1997, Congress added 21 U.S.C. § 360l (FDCA § 522). Under Section 522, FDA may order manufacturers of Class II or Class III products which are implantable products, life sustaining products or products for which a failure “would be reasonably likely to have serious adverse health consequences” to conduct post-market surveillance studies. These orders can be imposed as part of a PMA (or sPMA) approval or as part of a 510(k) clearance. FDA has the power to review the proposed post-market surveillance plan to ensure that it is adequate and is being implemented by qualified individuals.

Section 522 orders are in addition to, not in lieu of, other post-market authorities.

4. International Controls and Information

In addition to these U.S. centric obligations, companies are obligated to report adverse events reported from outside the U.S., to include adverse event information from non-U.S. sources in many submissions. The regulators also have information exchanges such that a product issue in one jurisdiction is reported to regulators in other countries. International or domestic information can trigger field actions in the United States, corrective actions by the manufacturer and detention or refusal of entry of imports.

There has been significant interest in registries. As detailed above, the agency has the authority through tools such as conditions of approval, special controls or Section 522 orders to mandate patient registries. In certain cases, registries can be

valuable post-market surveillance tools. This is particularly true with long term implantable products when one is looking for rare events or interactions. There are a number of registries already in place including, for example, registries for implantable cardiovascular devices such as pacemaker leads and stents. It is my understanding that a registry called ICOR is being implemented for certain orthopedic products.

This is not, however, a “one size fits all.” For many products, particularly lower risk, acute use medical devices, registries may provide little or no value. A registry for a strep throat diagnostic device would not be value added.

There are important issues that must be addressed in any registry. By definition, registries collect confidential patient information. As such, privacy must be maintained and true consent obtained. Not all patients want to be part of a registry. Linking registry participation with reimbursement raises serious questions about voluntariness.

In addition to identifying issues with medical devices, registries may also detect issues with health care providers (either institutional or individual). For example, there may be a cluster of issues

Recall Overview

FDA has a number of existing statutory mechanisms to address field issues. In a number of cases, these don't use the term “recall” but perform the functions of a recall.

1. Voluntary Recalls

In the event that industry takes a voluntary field action to address a product or regulatory issue, the company is obligated to inform FDA under 21 C.F.R. Part 7 and 21 C.F.R. § 806 within 10 days. The agency oversees the field action and conducts recall effectiveness checks of varying intensity based on the seriousness of the risk.

2. Mandatory Recalls and Notifications

If the company refuses to take action, FDA has a variety of actions it can take generally under 21 USC §360h (FDCA §518). These include the right to mandate a public notification if the device in question “presents an unreasonable risk of substantial harm to the public health” and notification is necessary to eliminate that risk. §518(e) also gives FDA the authority to order a mandatory recall in situations of a risk of serious adverse health consequences.

3. Seizure Actions

FDA also has the well established authority to conduct seizure actions pursuant to 21 USC §§331 and 334. In a seizure action, the government can go into the company and into the market place (including distributors and stores) and take physical control of the product to prevent any further movement in interstate commerce. Violation of a seizure order is a standalone criminal violation.

4. Publicity

Under 21 U.S.C. § 375, FDA has the authority to publicize issues or products which present an imminent danger to health or gross consumer deception.

5. Repair, replacement and refund

Section 518(b) gives FDA the authority to order the company to provide repairs or placements of defective products. FDA can also order a monetary refund to consumers. FDA has additional power under court decisions such as Lane Labs to order restitution to consumers.

6. Banning and suspension of approvals

FDA also has the authority under FDCA §516 and 515(e) to ban further distribution of products or to suspend (temporarily or permanently) PMA approval.

As can be seen, FDA has substantial statutory authority to take (or mandate) actions to protect consumers from unsafe products in the market. It is hard to imagine some action that FDA should be able to take action relating to an unsafe product in the market for which it does not already have statutory authority.

The existence of such authority is a very different question from whether FDA, industry and physicians are appropriately using or complying with such authority.

Recall Suggestions

There are, however, some ways in which the general recall process under 21 C.F.R. Part 7 and 21 C.F.R. § 806 could, in my opinion, be improved.

First, the term “recall” implies a physical removal or explants. That causes unnecessary patient anxiety and possibly unnecessary explants. It is also inaccurate. While in some cases a physical removal or explants may be the best medical course that is often not the case. Implying that the product should be physically removed can mislead patients. Of course one does not want to dilute or hide the importance of the field action. Calling it something like a “Safety Alert” while reserving the term “recall” for those situations in which a physical removal is appropriate conveys the seriousness of the situation in an accurate, non-misleading fashion.

Second, I would strongly encourage the agency to immediately classify the event so that the field notification can accurately state the seriousness of the situation. Assigning a classification six weeks after the physician notification is issued serves no physician or patient communication purpose and can mislead physicians and patients into thinking that there is a second recall when that is not the case.

Next, having more objective criteria for classification of recalls would improve the communication value of the classification.

Conclusion

Overall, products approved or cleared by FDA have very good safety records. Of course, all stakeholders should always be striving to improve on this already good record. Improvements in QSR (quality systems) offer the greatest impact.

FDA also currently has substantial post-market surveillance authority and recall authority. It is difficult to imagine actions that FDA may want to take when faced with a serious public health issue for which it lacks authority. Implementation and compliance by all stakeholders may well be the most fruitful area of focus.

Again, I appreciate the opportunity to present to the committee and would be happy to answer any questions.



**“A Delicate Balance: FDA and the Reform of the Medical
Device Approval Process”**

**Testimony before the Senate Special Committee on Aging
April 13, 2011**

David Nexon
Senior Executive Vice President
Advanced Medical Technology Association

My name is David Nexon, and I am Senior Executive Vice President of the Advanced Medical Technology Association (AdvaMed).

Thank you Chairman Kohl, Ranking Member Corker and Members of the Committee, for the opportunity to testify on this important topic. I would also like to especially thank you, Chairman Kohl, for your leadership on the Physician Payment Sunshine Act and for the opportunity you provided our industry to work with you to assure that the bill provided the public with the information it needed while enabling companies to continue to innovate.

AdvaMed is the world's leading trade association representing manufacturers of medical devices and diagnostics. AdvaMed member companies produce the medical devices, diagnostic products and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed members range from the largest to the smallest medical technology innovators and companies.

The U.S. Medical Technology Industry

The medical technology industry is an American success story. Our industry employs more than 400,000 workers nationwide, including over 14,000 in the state of Wisconsin, making Wisconsin one of the top 10 states with the largest medical technology industry employment. And, if indirect employment is included, the employment impact is substantially higher. Typically, for every worker our industry directly employs, another four workers are employed by businesses supplying components and services to our industry and our employees.¹

Other states represented by members of this Committee also have significant levels of medical technology employment, including Florida, Pennsylvania, and New York, which are all in the top 10 states with the largest medical technology industry employment.²

Our industry is heavily skewed toward small companies—the kind of companies that begin with a doctor, and engineer, and an idea to improve patient care. Almost two-thirds of the 7,000 medical technology firms in the U.S. have fewer than 20 employees. A high proportion of the breakthrough products in our industry come from these small, often venture-capital funded companies.³

And whether the firm is large or small, success in our industry comes only from innovation—the creation of diagnostics, treatments and cures that extend and enhance lives. Our industry's investment in research and development is more than twice the national average. Our product life-cycle is only 18-24 months.

The jobs our industry provides are good jobs—the kinds of jobs that allow employees to live the American dream. Industry pay levels are 38 percent higher than average pay for all U.S. employment and 22 percent higher than other manufacturing employment.⁴

While the number of manufacturing jobs was plummeting across the larger economy, even before the current recession, employment in our industry was expanding. Between 2005 and 2007, medical technology employment grew 20.4%, adding 73,000 jobs.⁵ During the recession, between 2007 and 2008, MedTech employment dropped 1.1 percent, compared to 4.4% for manufacturing as a whole.⁶

Our industry is so competitive that price increases have averaged only one-quarter the rate of other medical goods and services and just one-half the general CPI for almost 20 years.⁷

With \$33 billion in total exports in 2008, medical technology ranks eleventh among all manufacturing industries in gross exports.⁸ Notably, unlike virtually every other sector of U.S. manufacturing, medical technology has consistently enjoyed a favorable balance of trade. With the aging of both U.S. and foreign populations, the projected explosive growth of large middle class populations demanding modern health care in developing countries like China and India, and the accelerating pace of biomedical discovery, the potential for growth of our industry is great.

While we are very proud of our contributions to the U.S. economy, we are even more proud of our contributions to improving patient care. For patients, medical progress has been remarkable. Between 1980 and 2000, medical progress added more than three years to life expectancy. The death rate from heart disease was cut in half; the death rate from stroke was cut by one-third, and the death rate from breast cancer was cut 20%.⁹

While we are proud of the progress we have made in improving patient care and see immense future opportunities to provide jobs and contribute to long-term economic growth, we are also worried. Today, America is the world leader in medical technology. But the trends are not good. Ten years ago we were the unchallenged world leader. Today, we are the challenged world leader. In ten years, we may not be the world leader at all. As a recent PriceWaterhouse Coopers report showed, our lead is slipping on a number of dimensions of competitiveness.¹⁰ As I will discuss in more detail later in my testimony, a key factor in our loss of competitiveness has been the sharp decline in the efficiency of FDA's performance in stimulating the development of safe and effective medical devices and clearing them promptly so that they can be available to patients.

We are very appreciative of the Committee's interest in the topic of the Food and Drug Administration's regulation of medical devices. Put simply, FDA is a critical partner in our companies' efforts to bring safe and effective medical devices to patients. Without a strong, effective, and efficient FDA, we can not have a strong and competitive industry. President Obama recently noted in a Wall Street Journal opinion piece that there is a need to improve FDA's process for approving medical devices, "to keep patients safer while getting innovative and life-saving products to market faster." The predictability and efficiency of FDA decision-making, as well as reasonable, risk-based standards of evidence to assure the safety and effectiveness of medical technology products, is essential to drive new innovations for patients and for the long-term success of the medical device industry.

We are pleased at the President's recognition of the need to improve FDA's performance, and we are pleased that that recognition is shared by the FDA leadership. There are a number of policy changes now in process that, if implemented effectively, could significantly improve FDA's ability to meet the needs of patients and industry—but much needs to be done to restore the level of performance to where it was just a few years ago—a level that was suboptimal even then.

FDA's 510(k) Process for Pre-Market Review

FDA clears products for marketing by one of two routes—the 510(k) process or the Pre-market Approval (PMA) process. The 510(k) process clears products based on their similarity to products that are already on the market and is not available to highest risk products. To be cleared under the 510(k) process, a product must be judged by FDA to be “substantially equivalent” to a product already on the market, and manufacturers must demonstrate that the product is as safe and effective as the marketed product. If it has different technological characteristics or a different intended use than the product already on the market, the device manufacturer must present data to show that the product does not “raise new questions of safety and effectiveness.” The FDA has broad discretion to require any data that it thinks necessary to assure the substantial equivalence of the device, including clinical data. And the FDA is the ultimate arbiter of whether a company may utilize the 510(k) process as a route to market.

The 510(k) process is critical to a vibrant and successful device industry and to the process of medical innovation that provides better products for patients to address unmet clinical needs. In a typical year, 3,800-4,000 new products will be cleared for marketing through the 510(k) process. This compares to 30-40 products annually approved through the PMA process.

Of course, medical devices can be very complex and, like other medical treatments, involve a balancing of risks and benefits. Yet studies have shown that the 510(k) process has an exemplary record of protecting the public from unsafe devices. A recent study conducted by the Battelle Memorial Institute found that of the nearly 47,000 medical devices cleared by FDA through the 510(k) process and on the market since 1998, less than two-tenths of one percent were involved in a class I recall, the most serious level of recall. The Battelle study further noted that less than one-tenth of one percent of devices cleared via 510(k) since 1998 were recalled for design reasons, the type of issue likely to be observed during premarket review.¹¹

Another study by Professor Ralph Hall of the University of Minnesota, who is here with us today, found that class I recalls accounted for just 0.45 percent of cleared 510(k) products over the five years studied.¹² A third study by Dr. William Maisel, formerly of Beth Israel Deaconess Medical and now here with us today in his current role at the FDA, looked at all classes of recalls - the vast majority of which have no impact on patient care - and also found the 510(k) recall rate to be very low - in the range of 1.0 to 1.5 percent.¹³

These three studies come to the same conclusion - that FDA's 510(k) process has a strong safety record. While we recognize that product recalls do occur and that one patient harmed is one too many, our companies are striving - everyday - to make their products safer for patients, and we know that FDA shares this same goal.

The PMA process also has an exemplary safety record. Both the Hall and Battelle studies examined recalls for PMA products as well as 510(k) products and found a very low recall rate. Our joint challenge, as we seek to improve this excellent safety record, is to make sure that we do not impose requirements that provide minimal public health benefits while limiting the development of new treatments and cures.

Recently, FDA has undergone a thorough review of the 510(k) process, and is in the early stages of implementing some of their recommended changes. The Institute of Medicine has also been asked to review the process and will be making recommendations this year as to any changes it thinks are necessary. The device industry welcomes this review, because we believe that every process can be improved and that public confidence in it can be increased. In this regard, we have contributed a number of ideas to the FDA and are pleased to have engaged in positive dialogue with FDA.

The FDA has benefitted from significant increases in resources in recent years -- thanks in no small part to your leadership on the Appropriations Committee, Mr. Chairman -- and the premarket review process has been shown to have a strong safety record; yet troubling trends have emerged at the FDA that risk unduly delaying patient access to safe and effective products. These trends also increase uncertainty for companies and are negatively impacting investment in new treatments and diagnostics. For example:

- Average approval times for original PMAs have risen 75% just since 2007, to more than two years.¹⁴
- Our companies report that the time to get an Investigational Device Exemption (IDE) - the prerequisite to beginning the clinical trials that must be completed before a PMA application and some more complex 510(k) applications - have lengthened dramatically - to times that are often measured in years rather than months. And the time just to get a meeting to discuss an IDE can be six months or more.
- The average 510(k) decision time has risen 20 percent (97 days in 2002 vs. 116 days in 2008)¹⁵
- The number of days 510(k) submitters spend answering FDA requests for more data has nearly tripled (19 days in 2002 vs. 51 days in 2008)¹⁶
- The number of review cycles (the number of times FDA "stops the clock" on its review because it has decided to ask the manufacturer for more information) per 510(k) submission increased by one-third between 2002 and 2008 (1.4 per application in 2002 vs. 1.9 in 2008)¹⁷

- The percentage of 510(k)s withdrawn by sponsors has skyrocketed 89 percent from 2004 to 2009 (nine percent to 17 percent).¹⁸ This increase is indicative of a lack of clarity and consistency in FDA's review standards.

Additionally, several recent studies have demonstrated the existence of a "device lag" or a delay in U.S. patient access to innovative medical technologies as compared to patients in other countries. These studies outline a disturbing pattern of delay and inefficiencies at FDA that delay patient access to new treatments and cures and erode U.S. global competitiveness in the development of medical technology. Studies have also shown that these delays and inefficiencies do not result in greater protection for patients.

Dr. Josh Makower, medical device entrepreneur and professor at Stanford University, found in a recent survey of 200 small companies that on average, innovative new devices are available to U.S. patients two full years later than patients in other countries.¹⁹ In some cases, American patients wait as long as six years longer than patients elsewhere. This hurts patient health and U.S. competitiveness. Additionally, Dr. Makower's survey found that by strong majorities, companies reported that European regulatory authorities were more predictable and transparent than FDA. Almost half the companies reported that key FDA personnel responsible for reviewing their product changed during the course of the review, and one-third reported that appropriate staff was not present at meetings between the companies and FDA to discuss review issues. Companies are willing to work with the FDA and provide the data that are necessary for new product submissions, but it is unreasonable to expect a company to navigate rules that change in the middle of the game.

Similarly, the California Healthcare Institute, or CHI, recently released a report by the Boston Consulting Group called "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry" where they identified similar problems at FDA. Boston Consulting Group, using a different industry sample, found that the average lag between European and U.S. approval of PMA products had grown from slightly more than a year in 2004 to almost four years by 2010.

As I stated earlier, we are pleased that the Administration and the FDA, from the President on down, have recognized that there is a serious problem that needs to be addressed. Some of the proposals included in the 510(k) and "New Science" reform plans are very constructive could, if implemented properly, help improve the situation. These include greater reviewer training, more product specific guidance documents, and new efforts to improve the consistency of review. We are also pleased that some of the original proposals that could have increased industry burdens and further slowed product approvals without providing safety improvements were dropped from FDA's 510(k) implementation plan.

We stand ready to work with FDA in addressing these challenges.

FDA's Post-Market Authority for Medical Devices

FDA's work on ensuring patient access to safe and effective medical devices, however, does not end once products are on the market. No premarket review system, no matter how rigorous, will be able to identify all the potential problems that can develop in the real world of care for large numbers of patients with unique characteristics and with a wide range of health care professionals.

FDA has many post-market tools at its disposal, and its post-market authorities under the Federal Food, Drug and Cosmetic Act (FD&C Act) are robust. These controls ensure that all devices, but especially higher risk devices, are adequately monitored once they reach the market, and subject to remedial measures, if necessary, to protect the public health. In several respects, postmarket controls were tailored to reflect device risk and therapeutic or diagnostic importance, so that complex devices like robotic surgical equipment and automatic implantable cardioverters/defibrillators are subject to more controls than those applied to simple devices like stainless steel scalpels.

The following includes a description of the FD&C Act's three integrated types of device postmarket controls that assure device safety and effectiveness:

1. comprehensive sources of clinical experience data;
2. methods of device location to support remediation efforts; and
3. remedies to ensure the continued availability of safe and effective devices.

It is important to note that all devices are subject to the FD&C Act's General Controls that ensure devices and device manufacturing facilities remain in compliance. Once a device reaches the market, numerous regulatory requirements kick in requiring device manufacturers to actively monitor the performance of their products and ensure that their devices and manufacturing facilities maintain compliance with the requirements of the FD&C Act. For example, all devices, no matter what their regulatory classification, are subject to the general controls of the FD&C Act, including registering device facilities with the U.S. Food and Drug Administration (FDA) so that the agency may locate and inspect them, listing with FDA devices in commercial distribution, and manufacturing devices in accordance with the good manufacturing practices identified in the Quality System Regulation (QSR).²⁰ As part of the QSR, most devices are required to be manufactured in accordance with design controls, including appropriately managing any design changes made to a marketed device,²¹ an important part of ensuring safe and effective products.

The QSR also requires all device manufacturers to maintain complaint files on any alleged deficiencies related to a device's identity, quality, durability, reliability, safety, effectiveness, or performance.²² Manufacturers evaluate these complaints as part of their quality system to determine, among other things, whether medical device reports (MDRs) for device malfunctions and serious adverse events must be reported to the agency; corrective or preventive actions, including manufacturing changes, must be initiated; or

recalls must be undertaken. Complaint and corrective and preventive action files are among the first things FDA investigators examine when they inspect a device manufacturer; review of these documents provides enormous insight into the quality of a device manufacturing facility and the products manufactured at the facility.

The FD&C Act requires device manufacturers (and others) to collect and report to FDA a large amount of useful postmarket information. The FD&C Act and FDA's regulations require adverse event reporting to the agency through MDRs, thus providing FDA valuable information upon which to assess product performance. Specifically, a manufacturer must submit an MDR when it becomes aware of information that reasonably suggests that a device may have caused or contributed to a death or serious injury. MDRs must also be submitted for device malfunctions where, if the malfunction were to recur, the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury.²³ In addition to manufacturers, the FD&C Act requires importers and user facilities, for example, hospitals, to submit adverse event information to the agency. FDA receives MDR information within 30 days of manufacturers becoming aware of reportable events, unless remedial action is necessary to protect the public health, and then the time to report is reduced to five days. Non-compliance with reporting requirements can result in significant remedial action, ranging from criminal prosecution to product seizures. According to the agency, in 2010, it received about 330,000 adverse events for all medical devices.²⁴ FDA uses these reports to target unsafe or ineffective devices.

Importantly, the FD&C Act requires mandatory reporting of certain corrections and removals of devices within 10 working days of initiating remedial actions.²⁵ Device manufacturers and importers must report to FDA corrections or removals if the action was taken to reduce a risk to health posed by a device or to remedy a violation of the FD&C Act that may present a risk to health. As a result, all health-related voluntary recalls must be reported to FDA.²⁶ These reporting requirements also encompass non-recall actions, *i.e.*, corrections and removals of non-violative devices taken to reduce a risk to health.²⁷ Again, the failure to comply with this reporting requirement would potentially subject violators to dire enforcement consequences.

FDA also has ample authority to require postmarket studies to generate specific information the agency deems necessary to protect the public health. For example, FDA may require a post-approval study as a condition of approval of a premarket approval application (PMA) for a class III device.²⁸ Post-approval studies can be either clinical or non-clinical studies, or both. FDA's website currently identifies 120 records of post-approval studies ordered since January 1, 2005, and their status. The agency also monitors postmarket performance of PMA devices through the manufacturers' submission of annual reports that, among other things, contain a summary of unpublished reports of data from clinical or non-clinical studies, reports in the scientific literature concerning the devices, and changes made to devices that do not implicate safety or effectiveness.²⁹ A failure to comply with a condition of approval could result in grounds to withdraw an approved PMA.

Also, FDA has the authority under the FD&C Act to order postmarket surveillance for class II and III devices where (1) the device's failure would be reasonably likely to have serious adverse health consequences, (2) the device is expected to have significant use in pediatric populations, (3) the device is intended to be implanted for more than one year, or (4) the device is life-sustaining or life-supporting and is used outside a device user facility.³⁰ This postmarket surveillance requirement may last for three years, unless the agency and the manufacturer agree to a longer period, or if no agreement is reached, after a determination by a dispute resolution panel prescribed by statute. As an exception, postmarket surveillance for pediatric devices may last longer than three years.

Congress originally provided FDA with mandatory and discretionary postmarket surveillance authority in 1990, but after determining the law was "so broadly worded that it is causing a great deal of uncertainty about those devices which are subject to this requirement," Congress amended the law in 1997 to grant FDA "broad discretion to implement postmarket surveillance."³¹ Failure to comply with a postmarket surveillance order renders a device misbranded and is also a prohibited act under FD&C Act § 301(q). The agency's website currently identifies 39 postmarket surveillance studies.

For certain devices, FDA may impose additional postmarket requirements to ensure effective remedial actions. The FD&C Act gives FDA broad discretionary authority to require device tracking to ensure that manufacturers will be able to promptly locate devices in commercial distribution to facilitate patient or healthcare professional notifications or device recalls.³² Specifically, the agency may order a manufacturer to track a class II or III device where (1) device failure would be reasonably likely to have serious adverse health consequences, (2) the device is intended to be implanted for more than one year, or (3) the device is life-sustaining or life-supporting and is used outside a device user facility. Like the postmarket surveillance provision, Congress fine-tuned FDA's tracking authority in 1997 by eliminating mandatory tracking for certain devices because here also the "statutory mandate [had] proven to be uncertain with regard to which devices require mandatory tracking."³³ Currently, approximately 17 types of devices are subject to tracking orders, including TMJ prostheses, automatic implantable cardioverter/defibrillators, and ventricular bypass (assist) devices used outside a device user facility. A manufacturer that fails to meet the requirements of a tracking order misbrands its device.

FD&C Act § 520(j) and FDA's regulations authorize additional traceability requirements for certain devices. Specifically, manufacturers of implants and life-supporting or life-sustaining devices that can be reasonably expected to result in a significant injury to users if they fail to perform when properly used, must have procedures for identifying with a control number each unit, lot, or batch of finished devices and, where appropriate, components.³⁴ The purpose of these requirements is to support and facilitate corrective actions. This requirement by regulation applies to all devices within the specified categories, and unlike tracking, does not require FDA action to impose the product identification requirement to specific devices.

Importantly, the FD&C Act provides the agency with extensive remedial authority. To address devices in commercial distribution, the statute empowers FDA with more

remedial measures for devices than for any other FDA regulated product. For example, the agency has mandatory recall authority when there is a reasonable probability that a device would cause serious, adverse health consequences or death.³⁵ This authority empowers FDA to order the immediate cessation of use and distribution of devices prior to a hearing. Within 10 days, the agency would hold an informal hearing to determine the correctness of its original action or the exercise of administrative injunctive authority and whether a recall is appropriate. A failure to comply with a mandatory recall order misbrands the device and, of course, is subject to FDA's enforcement authority.

FDA rarely needs to invoke this authority because the vast majority of device recalls are conducted under the agency's voluntary recall guidelines that apply to all products regulated by FDA.³⁶ However, the regulatory threat posed by this authority reinforces the agency's leverage to obtain voluntary device recalls.

In addition to this powerful recall tool, the law authorizes FDA to issue mandatory notification orders that require notification to healthcare providers, patients, or others when a device presents an unreasonable risk of substantial harm to the public health.³⁷ Failure to comply with a notification order results in a misbranded device. Additionally, under the FD&C Act, FDA may order a device manufacturer, importer, or distributor to repair a device, replace a device, or refund the purchase price of a device if the device presents an unreasonable risk of substantial harm and the device was not properly designed or manufactured with reference to the state of the art.³⁸ The FD&C Act also empowers the agency to ban devices that present substantial deception or an unreasonable and substantial risk of illness or injury.³⁹

Importantly, FDA has powerful enforcement tools at its disposal, including criminal prosecution, device civil money penalties, injunctions, and device seizure.⁴⁰ Under the FD&C Act, and in support of device seizures or injunctions, FDA investigators can administratively detain devices based on a mere "reason to believe" that they are misbranded or adulterated.⁴¹ Further, the FD&C Act empowers FDA to publicize information relating to "imminent danger to health or gross deception of the consumer,"⁴² thus positioning the agency to leverage the vast amount of postmarket device information that the law directs to the agency.

The robustness of FDA's device postmarket authorities has long exceeded those for drugs. Recently, Congress updated drug postmarket authorities to make them more similar to those authorities long applied to devices, including tracking of prescription drugs⁴³ and the ability to order postmarket studies or clinical trials to assess serious risks related to the use of a drug.⁴⁴ However, the agency's postmarket drug controls still do not equal those for devices. For example, postmarket drug authorities do not include mandatory recall (including the device administrative injunctive component), reports of corrections or removals, or administrative detention. In sum, the FD&C Act includes more postmarket authorities for devices than drugs, and those comprehensive device authorities equip FDA to manage the device postmarket context.

Aside from the authorities listed above, FDA has a number of tools that are under development and will enhance their post-market abilities, including the implementation

of unique device identifiers, or UDI. The UDI system, particularly when coupled with electronic medical records and FDA's MedWatch program (Safety Information and Adverse Event Reporting), will provide FDA with the ability to track targeted patient outcomes for large patient populations on a real-time basis and can be an extremely valuable tool for device manufacturers anxious to improve their products and for FDA problem identification.

FDA is currently developing guidance on implementation of unique device identifiers, and AdvaMed is pleased to partner with FDA in this effort to develop a workable and effective tracking system.

Similarly, AdvaMed has been pleased to partner with FDA and other organizations as they have sought to develop and implement product-specific and patient outcomes-focused medical device registries. I'd like to focus for a minute on one particular example, which is our orthopedic sector's work on a national orthopedic registry.

AdvaMed's orthopedic sector is part of a collaborative initiative with orthopedic surgeons, hospitals, payers, patients, and other stakeholders to develop the American Joint Replacement Registry (AJRR). At the request of the AJRR Board of Directors, the sector has made a substantial and ongoing financial commitment to the AJRR, which has begun a pilot program, which is already collecting data in 15 hospitals before expanding nationwide. The AJRR's goal is to achieve over a 90% capture rate of all hip and knee joint replacements done in the U.S. by 2014. This registry is being thoughtfully developed by a multi-stakeholder governance board focused on the range of factors that impact patient outcomes after a joint replacement – including the implant itself, the skill and technique of the surgeon, and the facility in which the procedure takes place. The AJRR will generate data that can improve outcomes for hip and knee replacements and identify potential performance issues that require further investigation.

It is important to recognize, however, that registries are not a one-size fits all solution. They are costly and labor-intensive to operate. They require buy-in and willingness to devote substantial amounts of time from a large number of clinicians and hospital staff. In order to provide useful information, they must be designed to meet specific objectives and to collect data that relates directly to those objectives.

In summary, registries can play an important role in improving device safety and effectiveness under certain circumstances, but a more effective and less costly approach for most products is the use of UDI in conjunction with electronic medical records.

Conclusion

In conclusion, FDA's device regulatory systems must be thorough, timely and efficient in order to best serve both American patients and U.S. medical technology innovation.

AdvaMed and our member companies are supportive of a strong FDA so that it can fulfill its dual mission of patient safety and patient access to new treatments and cures.

I appreciate the Committee's interest in these issues and thank you for the opportunity to testify.

¹ The Lewin Group, "State Economic Impact of the Medical Technology Industry," June 7, 2010.

² *Ibid.*

³ United States International Trade Commission, "Medical Devices and Equipment: Competitive Conditions Affecting U.S. Trade in Japan and Other Principal Foreign Markets," March, 2007.

⁴ *Ibid.*

⁵ *Ibid.*

⁶ *Ibid.*

⁷ Donahoe, Gerald and King, Guy. "Estimates of Medical Device Spending in the U.S." May, 2009. Available from: <http://www.advamed.org/NR/rdonlyres/6ADAAA5B-BA37-469E-817B-3D61DEC4E7C8/0/King2009FINALREPORT52909.pdf>

⁸ The Manufacturing Institute, "The Facts about Modern Manufacturing," 2009, p. 18; ITC data web.

⁹ MEDTAP International, Inc. The Value of Investment in Health Care: Better care, Better Lives, 2004, Bethesda, MD: MEDTAP.

¹⁰ PriceWaterhouseCoopers, "Medical Technology Innovation Scorecard: The race for global leadership." January 2011.

¹¹ The Battelle Memorial Institute, "510(k) Premarket Notification Evaluation," Advanced Medical Technology Association, September, 2010.

¹² Hall, Ralph. "Using Recall Data to Assess the 510(k) Process." July 28, 2010. <http://www.iom.edu/~media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/06%20Hall.pdf>. April 11, 2011.

¹³ Maisel, William. "Premarket Notification: Analysis of FDA Recall Data." July 28, 2010. <http://www.iom.edu/~media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/05%20Maisel.pdf>. April 11, 2011.

¹⁴ The Boston Consulting Group, "Competitiveness and Regulation: the FDA and the Future of America's Biomedical Industry," California HealthCare Institute, February, 2011.

¹⁵ FDA data.

¹⁶ FDA data.

¹⁷ FDA data.

¹⁸ FDA data.

¹⁹ Makower, Josh. "FDA Impact on U.S. Medical Technology Innovation." Medical Device Manufacturers Association. November, 2010.

²⁰ Registration and listing are required per FD&C Act § 510 and the Quality System Regulation is found in 21 CFR Part 820.

²¹ 21 CFR § 820.30(i).

²² 21 CFR § 820.198.

²³ FD&C Act § 519(a).

²⁴ See Transcript of the Center for Devices and Radiological Health, Medical Devices Advisory Committee, Circulatory System Devices Panel at 39 (Jan. 25, 2011).

²⁵ FD&C Act § 519(g).

²⁶ A class I recall occurs when “there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.” A class II recall occurs when “use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.” A class III recall occurs when “use of, or exposure to, a violative product is not likely to cause adverse health consequences.” 21 CFR § 7.3(m).

²⁷ Corrections and removals without health-related implications are not reportable to FDA, but records of such corrections and removals must be maintained by a device facility for inspection.

²⁸ 21 CFR § 814.82(a).

²⁹ 21 CFR § 814.84(b).

³⁰ FD&C Act § 522.

³¹ S. Rep. No. 104-43 at 37 (1997).

³² FD&C Act § 519(e).

³³ S. Rep. No. 104-43 at 36.

³⁴ 21 CFR § 820.65.

³⁵ FD&C Act § 518(e).

³⁶ 21 CFR Part 7.

³⁷ FD&C Act § 518(a).

³⁸ FD&C Act § 518(b).

³⁹ FD&C Act § 516.

⁴⁰ FD&C Act §§ 302, 303, and 304.

⁴¹ FD&C Act § 304(g).

⁴² FD&C Act § 705.

⁴³ FD&C Act § 505D(b).

⁴⁴ FD&C Act § 505-1.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

**STATEMENT
OF
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FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SENATE SPECIAL COMMITTEE ON AGING

UNITED STATES SENATE

"A DELICATE BALANCE: FDA AND THE REFORM OF THE
MEDICAL DEVICE APPROVAL PROCESS"**

APRIL 13, 2011

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman, Ranking Member Corker, and Members of the Committee, I am Dr. William Maisel, Deputy Center Director for Science and Chief Scientist of the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to discuss the actions FDA is taking to enhance medical device safety, and our efforts to meet our public health goals of assuring the safety and effectiveness of medical devices while fostering innovation and important public health advances.

I joined CDRH last summer while the Center was in the midst of arguably the most comprehensive program review in its 35-year history. As part of this review, the Center has taken a hard look at how we conduct our business, how we utilize scientific information and make decisions, and how we can improve the health of American patients.

We have responded by taking strategic steps to strengthen our premarket evaluation and post-market surveillance of medical devices, while simultaneously promoting opportunities for medical device innovation. These steps will improve predictability, consistency, and transparency in our premarket and post-market programs and strengthen our scientific decision-making. However, we cannot do this alone.

Industry also shares a responsibility for the success of the review process and safety of medical devices. Data show that some companies submit poor quality applications, ask to meet with us but then ignore our feedback, or conduct poor quality clinical studies. This leads to unnecessary delays, wastes time and money for both industry and FDA, and exposes patients to unnecessary risks.

I am pleased to have this opportunity to provide an update on the important progress we have made in key programs at CDRH.

Background

I will begin with a brief overview of our regulatory authorities for medical devices. A medical device, as defined by federal law, encompasses several thousand health products, from simple articles such as tongue depressors and heating pads, to cutting-edge and complex devices such as implantable defibrillators and robotic equipment for minimally invasive surgery.

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) gave FDA specific authority to regulate the safety and effectiveness of medical devices. When FDA makes a risk-based classification determination for a type of device, it assigns it to one of three regulatory classes.

Class I is the lowest risk category of devices and includes items such as adhesive bandages. These are devices for which the general controls of the Act—which include establishment registration and device listing, compliance with current Good Manufacturing Practice and labeling, record-keeping, and reporting requirements—are sufficient to provide reasonable assurance of safety and effectiveness.

Class II is a medium-risk category of devices and includes devices such as intravenous catheters and powered wheelchairs. These are devices for which general controls, by themselves, are insufficient to provide reasonable assurance of safety and effectiveness of the device, and for which there is sufficient information to establish special controls, such as special labeling requirements, mandatory performance standards and post-market surveillance, to provide such assurance.

Class III is the highest risk category of devices and includes devices such as heart valves and coronary stents. Most Class III devices require approval of a premarket approval application (PMA) containing scientific evidence of the device's safety and effectiveness prior to marketing.

Devices must comply with the statutory standards for PMA approval, 510(k) clearance, or 510(k) exemption, all of which include considerations of safety and effectiveness. Most devices are cleared through the premarket notification [510(k)] process. FDA typically evaluates more than 4,000 510(k) applications and approximately 40 original PMA applications per year.

Improvements to the 510(k) Program

The 510(k) program is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that meet the statutory standards pertaining to safety and effectiveness, and fostering innovation in the medical device industry. In recent years, concerns have been raised both within and outside of FDA about whether the current 510(k) program optimally achieves these goals. In light of these concerns, and in keeping with the good government practice of periodically assessing the effectiveness of existing programs, FDA launched in September 2009 a two-pronged, comprehensive assessment of the 510(k) process to determine whether changes should be made to the program so that it can better achieve its goals. The first part of this assessment was the formation of two staff working groups—one to review the 510(k) program and make recommendations to strengthen it; the other to review how the Agency incorporates new science into its decision-making process and recommend how it can do so more predictably. As a second part of this assessment, FDA requested an independent evaluation by the Institute of Medicine (IOM). Established by the National Academy of Sciences, the IOM provides independent, objective, evidence-based advice to policymakers, health professionals, the private sector, and the public. The results of the IOM program evaluation are expected to be publicized this summer.

Importantly, FDA sought public input during both the development and review of the two internal reports. We engaged in extensive public outreach in developing and receiving

feedback on the preliminary proposals developed by the working groups, including two public meetings, three town hall meetings, three public dockets and many smaller meetings with different stakeholder groups. Final reports containing 55 recommendations were issued in August, 2010. In keeping with our commitment to transparency and stakeholder collaboration, FDA again sought public comment on the reports and recommendations before moving to its next step.

In January 2011, after reviewing public comment, the Agency announced actions it would take to strengthen the 510(k) process. FDA intends to initiate 25 actions implementing 47 of the 55 recommendations, including development of new guidance and enhancement of staff training. The Agency is also providing the IOM an opportunity to provide feedback on seven particularly complex recommendations before making a final decision on their implementation. For the recommendations being implemented, there will be additional opportunities for public input, where appropriate. For example, we held a public meeting last week to seek additional feedback on the recommendation to create an online repository of medical device labeling to include photographs that would provide easier access to important health information for patients and health care professionals, without breaching manufacturers' product trade secret information.

Implementation of our 510(k) action plan will improve product safety. For example, the recommendation to issue guidance on clinical study design will strengthen the design and performance of premarket clinical trials used to assess medical device safety and effectiveness. As part of the action plan, CDRH is also implementing a standard practice

of issuing “Notice to Industry” letters to allow the Agency to more quickly inform stakeholders of new safety concerns, or to clarify evolving regulatory expectations in response to new scientific information. Finally, FDA is strengthening collection and analysis of post-market information by modernizing its information technology (IT) infrastructure, and by developing better data sources, methods, and tools for analyzing meaningful post-marketing information.

The 510(k) and Science workgroup reports, recommendations, and useful related links are all available on FDA’s website at

<http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm239448.htm>.

Innovation Initiative

In addition to our review of the 510(k) program, we recently announced the Medical Device Innovation Initiative to accelerate the development and regulatory evaluation of innovative medical devices and strengthen the nation’s research infrastructure for developing breakthrough technologies and advancing quality regulatory science. As part of this initiative, FDA is proposing additional actions to encourage innovation, streamline regulatory and scientific device evaluation, and expedite the delivery of novel, important, safe and effective innovative medical devices to patients, including:

- Establishing a priority review program for pioneering technologies;

- Establishing a voluntary, third-party certification program for U.S. medical device test centers designed to promote rapid improvements to new technologies during a product's development and clinical testing stages;
- Creating a publicly available core curriculum for medical device development and testing to train the next generation of innovators;
- Better leveraging of device experience and data collected outside the United States; and
- Engaging in formal horizon scanning—the systematic monitoring of medical literature and scientific funding—to identify and predict important advances in technology, in order to prepare for and respond to transformative innovative technologies and scientific breakthroughs.

Medical Device User Fee Act Performance

While the Agency continues its efforts to improve the 510(k) program and encourage product development, FDA's device review performance has been consistently strong. As FDA's FY2010 Medical Device User Fee Act Performance Report to Congress indicates, 95 percent of the over 4,000 medical device applications subject to user fees that FDA reviews every year (FDA reviews over 9,000 submissions annually) are reviewed within the goals that were agreed to by the medical device industry under the Medical Device User Fee Amendments of 2007 (MDUFA). Under the 510(k) program—the pathway used for 90 percent of the devices we examine each year—90 percent of our

reviews were completed in 90 days or less, and 98 percent of reviews were completed in 150 days or less, as we committed to do under MDUFA.

There are a limited number of areas in which we are not meeting the goals agreed to with the industry, although our performance in those areas is generally improving. This is the result of several factors, including increasing workload, turnover of key staff, growing device complexity, and poor-quality submissions. The number of applications for premarket approval and panel-track supplements (for "breakthrough" devices) has increased by 48 percent over the past two years. In addition, medical devices are becoming more technologically complex, as reflected by the growing number and variety of technical experts that FDA must consult during the review process. Finally, a significant number of submissions received by the Agency are incomplete or fail to address basic elements, such as the device's description or proposed indications for use. Based on a recent analysis we performed, more than half of the 510(k) submissions received by FDA have quality problems. Although FDA is meeting its performance goals for 510(k)s, these submission quality problems delay the completion of the marketing clearance process and unnecessarily divert resources from more productive activities in the review process. The current legislative authority for MDUFA, reauthorized in 2007 by the FDA Amendments Act (FDAAA), will expire in September 2012. Accordingly, FDA has been holding public meetings and conducting discussions with both regulated industry and stakeholder groups in developing recommendations for reauthorization of this critical program.

Post-market Surveillance Activities

FDA recognizes the importance of post-market surveillance (PMS) and utilizes a multi-faceted approach to monitor the performance of medical devices after marketing clearance or approval to ensure their continued safety and effectiveness. FDA uses several PMS tools to accomplish effective monitoring of device performance. For example, the Agency requires medical device manufacturers to follow certain PMS requirements for marketed devices, including adverse event reporting for all devices, and tracking systems and post-market surveillance studies or post-approval studies for select devices. This approach provides for nationwide surveillance through adverse event reporting, complemented by targeted efforts, such as post-approval studies. However, medical devices present unique post-market challenges because of their diversity and rapid product evolution. Importantly, key infrastructure improvements, such as increased electronic adverse event reporting, the establishment of the Unique Device Identification (UDI) system, and the incorporation of UDI into health-related electronic records, will have a profound and positive impact of the nation's ability to adequately monitor medical devices in the post-market period.

Mandated Post-market Studies

FDA currently has two authorities with which to require manufacturers to conduct postmarket studies: post-approval study (PAS) authority under section 515 of the Act, and PMS authority under section 522 of the Act. PAS authority allows FDA to ask a device manufacturer to conduct a study (or studies) of a PMA device, as a condition of its

approval, to address product performance in the post-market period (e.g., long-term safety). Consistent with the Agency's transparency initiative, overall study status, including study results for completed studies, are posted on FDA's website.

Authority under section 522 allows FDA to require post-market surveillance studies for certain Class II or Class III devices, for example to address significant public health issues that arise in the post-market period. Section 522 studies may be required for certain categories of devices, including implants and devices expected to have significant use in pediatric populations.

Over the past two years, the program has significantly expanded, and there are currently 38 section 522 studies in process. There are a total of 337 PAS requirements. FDA carefully monitors manufacturer compliance with their post-market responsibilities. As of April 6, 2011, 290 studies (86 percent) are in compliance [this includes 150 completed (44 percent) and 140 ongoing (42 percent)]; 47 studies (14 percent) are out of compliance. Reasons for studies being out of compliance include failure to progress according to the agreed upon timeline (46) and failure to agree on a protocol within six months of PMA approval. In addition, we have developed a PAS Inspection Program to audit select PASs for possible violations of applicable regulations. Failure to comply with a required PAS or a section 522 Order can result in regulatory action including, but not limited to, a warning letter, seizure, injunction, and/or civil money penalties.

Adverse Event Reporting

FDA uses two principle systems to capture device-related adverse event and product problem reports: the Medical Device Reporting regulation (MDR) and the Medical Product Safety Network (MedSun).

MDR is the mechanism by which FDA receives over 300,000 significant medical device adverse events from manufacturers, importers, and user facilities annually. FDA carefully evaluates the reports received to identify safety concerns of public health importance. FDA recognizes the limitations inherent in passive reporting systems such as MDR, including underreporting of adverse events and the submission of incomplete or difficult-to-understand reports. Many reports lack sufficient information to accurately identify the product in question. FDA works with reporters to partially offset this limitation. In addition, the UDI system under development, described below, will help overcome this shortcoming.

Recognizing the shortcomings of passive reporting systems, FDA launched MedSun in 2002. MedSun is an "active" adverse event reporting program that allows FDA to work collaboratively with the clinical community to identify, understand, and solve problems with the use of medical devices. Over 350 health care facilities, primarily hospitals, participate in the MedSun Network. The Agency has continued to develop its MedSun regional representative program, comprised of trained MedSun representatives, including physicians and nurses having expertise in risk management, patient safety, quality improvement, biomedical/clinical engineering, materials management, and surgical services, who facilitate on-site data gathering, and will focus on efforts to automate

detection and reporting, and improve outreach to user facilities in the MedSun system to stimulate user facility reporting.

Data Mining

To complement individual review of adverse event reports, FDA has implemented data mining capabilities which, based on automated statistical algorithms, can detect potential safety signals among the hundreds of thousands of reports received annually. Early experience in piloting these capabilities with select device groups has proved promising. Efforts are currently underway to evaluate the use of data mining for all device malfunction reports which comprise over 60 percent of all adverse event reports.

Device Recalls

A medical device recall is a method of removing or correcting products that are in violation of laws administered by the Agency, and can serve as a mechanism to advise patients and healthcare providers about dangerous devices that are defective or otherwise improperly marketed.

Role of Industry in Recalls

Generally, a recall is triggered when a manufacturer recognizes that a product failure requiring a recall exists. A product failure can include problems such as design flaws, errors in labeling or defects introduced during the manufacturing process. In most cases, firms that market defective or otherwise violative devices recall them voluntarily, often following discussion with FDA of the Agency's concerns about their products.

Role of FDA in Recalls

FDA has authority to compel recalls of medical devices that pose significant risks of injury or death to patients. While this authority is a critical public health protection, the Agency has only had to use this authority sparingly, such as when a manufacturer fails to voluntarily recall a device that is a serious health risk. Once the device recall process is initiated by the firm, FDA classifies, coordinates, and monitors the recall.

The success of FDA's device recall efforts requires prompt notice to patients and health care professionals and efficient recall classification. CDRH is leading a range of transformative projects to build its strength in these areas.

In fall 2010, CDRH began its Recall Process Improvement project to enhance the efficiency and clarity of the medical device recall process. In March 2011, staff developed strategies to improve notification and classification of recalls. These strategies include educating industry on recall documentation and reporting, improving efficiency of communication between Agency components, and standardizing the recall classification processes. Further, the Agency has improved its internal tracking of device recalls.

FDA continues its effort to assist manufacturers and is planning an online educational tool focusing on recalling firms' reporting obligations. Educating industry on the information required to be submitted following initiation of a recall will result in more

timely and complete recall documentation. Finally, as requested by industry, FDA is preparing a guidance document that clarifies the difference between modifying a device to enhance safety to respond to adverse events, and a modification to correct a violation. CDRH anticipates issuing the guidance document by August 31, 2011.

Registries

FDA takes a proactive role in fostering registry development. FDA has worked with multiple stakeholders to begin, or further the development of, many national registries, and is currently involved in over 20 registry efforts. These include, among others, an anaplastic large cell lymphoma (ALCL) registry to collect information regarding cases of breast implant-associated ALCL; the Improving Pediatric and Adult Congenital Treatments registry on transcatheter procedures and devices used to treat congenital heart disease; and the National Implantable Cardioverter Defibrillator registry, which has expanded to identify adverse events associated with defibrillator leads. In addition, registries are often used in the conduct of mandated post-market studies. Currently, there are over 60 PAS studies that involve registries.

FDA is leading an effort to develop and implement a national strategy for the best public health use of health-related electronic data that incorporates UDIs and leverages existing procedure and device registries. A workshop addressing the issues and challenges involved with incorporating UDIs into health-related electronic records is planned for this year.

FDA has also recently led efforts to link national registry data with Center for Medicare and Medicaid Services claims data to study the safety of drug-eluting coronary stents, endoscopic vein harvesting for coronary artery bypass grafting, and transmyocardial revascularization for intractable angina. Further linkage capabilities will be explored this year under the Sentinel Initiative.

Medical Device Epidemiology Network (MDEpiNet)

The MDEpiNet Initiative was launched in 2010 to create collaborations with academic centers that have epidemiologic, statistical, and clinically relevant expertise. This established network will join with FDA experts to address evidence gaps and develop innovative approaches for conducting robust studies to improve FDA's understanding of the safety and effectiveness of medical devices throughout their life cycles. This public-private partnership will involve other stakeholders, such as other public health agencies, data holders, and consumer representatives, and will leverage their collective expertise to significantly improve the credibility, relevance, and efficiency of clinical research regarding medical devices. Evidence synthesis will be an important component of MDEpiNet. As medical devices move through their total product life cycles, there is a need to continually update their benefit/risk profiles in the context of new scientific evidence. Advances in epidemiologic and statistical methods and information technology now permit access to, and synthesis of, evidence available from varied data types and data sources including clinical trials, PASs, registries, health-related claims data, and published literature.

Unique Device Identification (UDI)

Section 226 of FDAAA of 2007 directs FDA to promulgate regulations establishing a UDI system for medical devices. FDA is developing a proposed regulation to issue in 2011. The system established by the rule, once finalized, will require the label of every medical device to bear a UDI, except where the rule provides for alternative placement of the UDI or provides an exception for a particular device or type of device. The UDI Database, which will be built and maintained by FDA, will contain identifying information about the device. It will not contain any patient information.

Establishment of a UDI system is of critical importance in fulfilling the promise of a robust and multi-faceted PMS effort. Health-related electronic data from large data sources, such as health insurers and integrated health systems, contain a wealth of public health information that could be harnessed to contribute to understanding device safety and effectiveness. Currently, however, these data cannot be used to identify specific device exposures in patients. A vast amount of potentially useful data regarding patient safety and outcomes remains untapped. Incorporation of this key data element will greatly facilitate many important public health-related activities including:

- reducing medical errors;
- reporting and assessing device-related adverse events and product problems;
- facilitating recalls;
- assessing the benefit/risk profile of medical devices in large segments of the U.S. population;
- post-market surveillance;

- tracking and tracing;
- anti-counterfeiting/diversion;
- import review;
- disaster/terror preparation; and
- anticipating and tracking product shortages.

Recognizing the transformative nature of UDI, FDA is developing the IT infrastructure necessary to support the effort, including the creation of a searchable UDI database that will serve as the authoritative source for all UDIs and UDI-related information. FDA is planning to award a contract for UDI database development in 2011. FDA is also planning to incorporate UDIs into adverse event reporting and to link UDIs to manufacturer registration and product listing to facilitate adverse event analysis and identification of important safety signals. Furthermore, pilot efforts are underway to incorporate UDIs into other registries that are early in their development. FDA is also hosting a workshop this year to identify opportunities and challenges involved with incorporating UDIs into health-related electronic records.

Sentinel Initiative

FDA's Sentinel Initiative is aimed at fostering the development and use of a national infrastructure of electronic health care data systems for medical product safety surveillance. Sentinel will transform FDA's ability to track the safety of all FDA-regulated products, complementing existing systems such as those previously discussed. The incorporation of UDI into these data sources will greatly advance the device

component of the Sentinel Initiative and improve our understanding of the risk/benefit profile of medical devices. For active surveillance to be truly robust, longitudinal patient records are needed. As mentioned previously, registry data can be linked to longer-term data, such as claims data, to create longitudinal patient care profiles while adhering to existing standards for ensuring patient privacy. Within Sentinel, efforts are currently underway to explore best methods for linkages, as well as development of common data models across claims data sources and validation studies of claims-based outcomes. Sentinel is well-suited to such inquiries and development of optimal active surveillance efforts.

Government Accountability Office (GAO) Evaluations

In January 2009, GAO identified medical products safety in its High-Risk Series, in part, because of FDA's growing responsibilities, increasing product complexity, and the marked globalization of the medical products industry. FDA recognizes the challenges that GAO identified and is taking affirmative steps to implement measures designed to address GAO's identified concerns. For example, CDRH has taken important steps to strengthen post-market monitoring of device performance.

GAO has also cited FDA's failure to fully implement the requirement in the Safe Medical Devices Act of 1990 to either reclassify the remaining Class III pre-amendments device types (devices that were on the market on or before May 28, 1976) that are allowed to enter the market through the premarket notification process, or require PMAs for these devices. Since that report was issued, FDA has been addressing this concern using a risk-

based approach. Of the original 140 Class III 510(k) pre-amendment devices identified, only 26 remain subject to 510(k). CDRH is actively evaluating all 26 of these products, according to the process required by regulation, and expects to down-classify or require PMA's for the remaining products by the end of 2012.

CONCLUSION

FDA evaluates thousands of medical devices annually and the vast majority of these devices perform well and improve patient health. Through our recently completed comprehensive programmatic review, FDA is taking actions to further strengthen our scientific decision-making to increase the predictability, consistency, and transparency of our processes and policies, and to revolutionize the way we conduct postmarket surveillance. Through smarter device regulation, our efforts are already starting to pay off. In the last year, for example, we identified and addressed safety concerns affecting drug infusion pumps, automated external defibrillators, and medical imaging technologies that emit radiation, such as CT scanners. FDA's medical device center will continue to support the United States' position as the leader in safety, medical device technology, and innovation, and make good on our commitment to promoting and improving the health of the American public.

Mr. Chairman, this concludes my formal remarks. I will be pleased to answer any questions the Committee may have.

**A Delicate Balance:
The Food and Drug Administration and
Reform of the Medical Device Approval
Process**

Senate Special Committee on Aging
April 13, 2011

Statement Submitted by
Terrie Cowley, President,
The TMJ Association, Ltd.

I am Terrie Cowley, President of The TMJ Association, a Wisconsin-based non-profit patient advocacy organization. Our mission is to improve the quality of health care and lives of everyone affected by Temporomandibular Disorders (TMD).

My thanks go to you Chairman Kohl as well as to you, Senator Corker for convening this extremely important hearing focusing on FDA's medical device approval and Postmarket Surveillance processes. These processes determine how the FDA carries out its mission to protect the American public who depend upon the FDA to assess the safety and efficacy of medical devices. I trust the following account provides insight into how government agencies, including the FDA, professionals, and professional organizations continually shirked their responsibility to protect the TMJ implant patients of this country.

What are Temporomandibular Disorders?

Temporomandibular disorders are characterized by pain in the jaw area and/or dysfunction of the temporomandibular (jaw) joints.¹ They represent a family of disorders mediated by genes, age, sex, and environmental triggers.¹ Most patients have pain in the joint area, neck and shoulders, but may show little or no joint pathology. Some patients do exhibit joint pathology, which may be the result of injury or conditions that routinely affect other joints in the body, such as arthritis. However, in addition to the jaw pain, many TMD patients, who are primarily women in their child-bearing years, experience other chronic pain conditions, such as fibromyalgia, chronic fatigue syndrome, chronic headache, and vulvodynia.² Needless to say, the existence of comorbid conditions increases the complexity and difficulty in diagnosing TMD, much less in finding safe and effective treatments in a health care system where these associated conditions lack a medical home. As yet there is little scientific understanding of what causes TMD and why these disorders progress in some patients. Nevertheless, this has not prevented practitioners from proposing over 50 different treatments and a range of medications, with little scientific scrutiny to establish their safety or efficacy. Currently, there are no standards of care applicable to the diagnosis or treatment of TMD patients.³

A 2010 National Institutes of Health publication, *TMJ Disorders*, states, "Surgical treatments are controversial, often irreversible, and should be avoided where possible. There have been no long-term clinical trials to study the safety and effectiveness of surgical treatment for TMJ disorders. Nor are there standards to identify people who would most likely benefit from surgery."⁴ What we at The TMJ Association do know from our patient base is that increasing surgeries typically result in increasing pain and dysfunction, actually, even death. Unfortunately, these increased surgeries often lead to an implant to replace the jaw joint, about which the NIH comments; "Surgical replacement of jaw joints with artificial implants may cause severe pain and permanent jaw damage. Some of these devices may fail to function properly or may break apart in the jaw over time. If you have already had temporomandibular joint surgery, be very cautious about considering additional operations. Persons undergoing multiple surgeries on the jaw joint generally have a poor outlook for normal, pain-free joint function."⁴ This may explain the death of Margaret Rose Hutchison, of South Park, PA, who had multiple TMJ implants and died at the age of 41 after her 62nd jaw surgery.⁵

Why the Jaw Joints are Special

The pair of temporomandibular joints are located at the base of the skull amidst the most sensitive and vulnerable areas of the head, at the convergence of the body's major cardiovascular, neurological, auditory and ocular systems. The joints allow us to talk, eat and swallow and make facial expressions that reflect every emotion. They are the most complex joints in the body, unique in their composition and unique in that they always work as a pair. They are controlled by four sets of chewing muscles that enable three-dimensional movements: up and down, side to side, and forward and back.⁶ When trauma or pathology results in destruction or degeneration of joint tissue, an artificial joint may be implanted in hopes of restoring function.

TMJ Implants: The Recent History

Since the mid-1960s, a variety of materials have been used to replace all or parts of the temporomandibular joint. Sometimes surgeons replace the soft tissue disc, which acts as a shock absorber between the head (condyle) of the lower jaw bone (the mandible) and its insertion into the temporal bone of the skull, allowing the mandible to glide smoothly during movements. The disc replacements are frequently called interpositional implants (IPI). In other instances, a mandibular component with condylar head, the fossa (the depression in the temporal bone of the skull into which the condyle fits) or both, are replaced with prosthetic devices.

Most biomaterials for jaw joint reconstruction were on the market before passage of the 1976 Medical Devices Amendment Act. That act required manufacturers to provide evidence that their devices were safe and effective. However if new TMJ implants to be marketed after 1976 were shown to be "substantially equivalent" to a pre-Amendment device, the law allowed them to be sold without testing. This is known as the 510K process. Two synthetic materials that have been widely used as disc replacements for torn or displaced natural TMJ discs are Dow Corning Silastic (based on Silicone) and the Vitek, Inc. Proplast-Teflon implant.⁷

Dow Corning Products

Silicone implants appeared in several forms. The first, introduced in the mid-sixties, was a block that was carved to disc shape. Another was Silastic H.P. sheeting reinforced with Dacron. In 1983 the FDA approved the Dow Corning Silastic TMJ implant H.P. based on substantial equivalence (510K) to Silastic Sheeting marketed prior to 1976. This implant had been designed by Dr. Clyde Wilkes for temporary use only and was made with "tabs" facilitating removal after several months. He was aware that complications arose from long-term implantation of Silastic in the jaw joint.⁷

The TMJ Association has heard from patients who have had an array of Silicone implants, the most common being the disc made of Silastic H.P. sheeting. However, other Silicone blocks designed to reconstruct toes and testicles have been implanted into patients' jaw joints.

Short-term studies on Silastic in the seventies looked good. However, after one to five years there were reports showing substantial problems including ankylosis, arthritis, and lymph node swelling.⁷ A 1986 article reported "fragmentation, perforation, and deterioration of the Silastic material."⁸ And another stated that, "Silicone may not be a totally inert material and that its biomechanical properties are not ideal for use in the TMJ."⁹ By the end of the 1980's enough

failures had occurred for some researchers to call for strict limits on the use of Silastic.¹⁰ One 1992 study warned surgeons that implant particles could migrate from the disc site and that they should be alerted to possible systemic reactions and foreign body synovitis, which would hasten implant failure.¹¹

Dr. Mark Lappe, Professor of Health Policy and Ethics at the University of Illinois, provided testimony in 1992 at a Congressional hearing, *Are FDA and NIH Ignoring the Dangers of TMJ Implants?* He stated, Dow Corning's public documents and a review of the literature indicated that "as early as the sixties they saw foreign body giant cell reaction and knew it induced fibrosis and calcification.⁷ But, even in the late seventies and early eighties, with the knowledge of the adverse effects of the wear particles, Dow Corning issued no adequate warning in the package insert and continued marketing the implants.¹² Dow Corning knowingly allowed their Silicone sheeting to be used for restoring the damaged TMJ even though it was highly likely that the sheeting, even when reinforced, could not stand up to the stresses typical of a major, pressure-bearing, inflammation-damaged joint."¹³ As late as 1989 there had not been a single long-term study of the use of Silastic in animals or humans.⁷ In 1991 when sheep studies were conducted, severe bony destruction and foreign body giant cell reaction were found. Finally, after twenty years of use in humans, it was decided that Silastic isn't appropriate for long-term use and that even short-term use is highly problematic. In 1993 Dow Corning exited the TMJ business. To date no company has submitted a Premarket Application for the use of Silastic in the Temporomandibular joint, however it is being used off-label by oral surgeons.

Vitek, Inc.: the Proplast-Teflon Disaster

In the seventies, Vitek, Inc. developed and sold Proplast sheeting (Teflon FEP film laminated to a porous composite material made from polytetrafluoroethylene (PTFE) and carbon).⁷ When the carbon blackened the whites of the implant recipient's eyes, the implant was modified and the Teflon film was laminated to PTFE and aluminum oxide.⁷ These implants, like the Silastic IPIs, were usually no larger than a thumbnail and were manufactured individually or custom-cut from sheets in the operating room by the surgeon, and then sutured to the fossa.⁷ Vitek also manufactured a TMJ total joint device coated with PTFE as well as other facial implants.

As with the Silastic implants, early reports claimed success, and in 1983, the FDA notified Vitek president and founder Dr. Charles Homsy, that the IPI was deemed equivalent (510K) to a device marketed prior to May 28, 1976. Three years later, however, at the 1986 meeting of the American Association of Oral and Maxillofacial Surgeons (AAOMS), several surgeons reported catastrophic biomechanical failure of the Vitek IPI causing a giant cell reaction that led to bone resorption and pain. A summary of the literature from 1986 to 1991 reported a failure rate of 10 to 25 percent and by 1992 a success rate of less than 20 percent was being reported.¹⁴

As early as 1963, Sir John Charnley, the acknowledged father of hip implant surgery, reported in the orthopedic literature on the failure of Teflon when used in hip prostheses, citing fragmentation, giant cell reaction and bony changes.¹⁵ Certainly, "the orthopedic experience could have predicted the long-term results described in the oral and maxillofacial surgery literature decades later."⁷

Nor is that all. Only after reports of the Teflon implant failure began appearing in 1984, were animal studies conducted on dogs. The results were “essentially catastrophic,” according to a 1990 deposition that Dr. Jack Kent, a Vitek consultant, who also owned 21,000 shares in the company, gave in an Arizona court case against Vitek.⁷ After just a few months, the Teflon layer was “completely worn” and Teflon particles had triggered bone erosion in the dogs.⁷ Dr. Kent wrote a letter to Dr. Homsy in early 1984 expressing his concern that, based on what he found when he explanted an IPI from one of his patients, Vitek might have a “calamity of unbelievable proportions on our hands.”¹⁶ This did not deter Dr. Kent from continuing to write articles praising the Vitek implants or stop him from collecting royalties.

Though the FDA had been hearing about adverse problems related to the Vitek implant at least by 1986, because of a mix-up with their Medical Device Report (MDR) Program, the reports had been dismissed.¹⁷ By 1988 they “had received information from experts that the Vitek implants were failing and needed to be explanted, and that the patients with explanted devices were worse off than they had been before treatment. Problems included excruciating pain and the degeneration of parts of the skull,”¹⁷

In August 1990 FDA finally took action and rescinded the 510K for Vitek’s TMJ devices and on January 7, 1991 the FDA issued a Class I recall. However, in June 1990 Vitek declared bankruptcy, Charles Homsy moved patents off shore, and in March 1992 fled the country for Switzerland, leaving the FDA to handle the recall.

FDA and the Recall

The Class I recall of the Vitek products was the first time it fell to the FDA to conduct the recall of a device since passage of the 1976 Medical Devices Amendment Act. Not only was this because the manufacturer had declared bankruptcy, but also because he had left the country leaving inadequate records of sales behind. Considering the gravity of the situation the possibility of what FDA called “open communication to the brain,” one would have hoped that the FDA would pursue every option to reach out to potentially affected patients. Instead, the agency turned to the professional oral surgery organizations. Members of AAOMS received a copy of the FDA “Safety Alert” concerning these implants.⁷ Later, in a “Public Health Advisory,” surgeons were asked to notify their patients, discuss the risks of device failure, and continue to monitor them.⁷ In addition, they were told to encourage their patients to enroll in Medic Alert’s International Implant Registry.⁷ The surgeons were given 30 days to complete Patient Notification Confirmation forms regarding the action they had taken.⁷ A year later, only 312 patients had been registered with Medic Alert and the registry was discontinued. Less than 200 notification forms had been received from surgeons.⁷ This, in spite of an estimated 26,000 Vitek IPI’s had been sold and that some 87,000 sheets and blocks had been marketed, which oral surgeons could use instead of individual IPIs.

At the time of the Vitek FDA recall the FDA initiated a media blitz, not about the Vitek devices, but about misbranded orange juice—not orange juice that would harm anyone, just that the labeling misrepresented the ingredients. The TMJ Association begged the FDA to do the same for a device that could enter one’s brain but to no avail.

The oral surgeons practiced damage control. In 1993, with a 20/20 segment on TMJ implants imminent, AAOMS hired one of the country's top public relations firms to run interference for them. In an urgent and confidential memo AAOMS discussed how fortunate that the 20/20 broadcast would air opposite game three of the American League Championship Series.¹⁸

Almost all of the implant patients who contacted The TMJ Association said that they had never heard about the Vitek recall from their implanting surgeons. It appears that many dentists denied that the implants could cause the problems experienced by the patients, often blaming them and recommending that they get psychological help. Patients' records were lost and in one case, every piece of evidence of the procedure, including hospital and insurance records, were erased. It was only when this patient moved to another state and had imaging studies done that her implant was confirmed. The patients had been lied to and abandoned, left without care, and in many cases, were unable to find another surgeon to care for them. We have photos of patients who had a total joint device that had broken through their skin and had been exposed for up to four years before they were able to find a surgeon to help them. Last year, twenty years after the recall, we heard from several patients who had Vitek implants, subsequent surgical procedures, and increasing health problems and were never told the Vitek devices had been recalled.

Total Jaw Joint Devices

Considering the harm associated with the Vitek and Silastic implants of the eighties and nineties, one would have thought that the FDA would be hyper vigilant in reviewing TMJ total joint devices for approval. That was not to be.

In 1999 FDA called for Premarket Approval Applications (PMAs) from companies manufacturing devices for implantation into the jaw joint. Two companies submitted applications: TMJ Concepts and TMJ Implants, Inc. In 2002 Lorenz Surgical, a subsidiary of Biomet Inc., submitted a PMA.

In 2006 the General Accountability Office (GAO) was asked by members of the US Senate to investigate the FDA approval process of TMJ devices. Their report, published in 2007: *FDA's Approval of Four Temporomandibular Joint Implants*, noted that the FDA looked at study protocols, patient follow-up, engineering testing, and other issues, such as device labeling, and found that all implant PMAs had similar deficiencies, such as inadequate patient follow-up, making it difficult to determine outcomes over time.¹⁹

Nevertheless the FDA "conditionally" approved all the devices, requiring sponsors to comply with specific FDA conditions to obtain full approval.¹⁹ These included conducting Post Market Surveillance and collecting data on patients for at least three years. To determine how FDA monitored compliance, the GAO reviewed the annual reports that the FDA required from the companies. These reports were to include information on their Post Market Surveillance Studies and other requested data. Although a total of 18 annual reports should have been submitted to FDA by 2006, only 13 had been received by the agency and of those 13 seven lacked sufficient information for the FDA to judge compliance.¹⁹ In detail, here is how each company complied with FDA demands:

TMJ Concepts

- The PMA found the clinical study to be observational without a protocol. From a statistical perspective, the study was seriously flawed. From a bioengineering perspective, the device should not pose problems.
- Though many annual reports were missing from TMJ Concepts,¹⁹ FDA was able to review the two annual reports submitted by the sponsor in 2000 and 2004. For both reports, TMJ Concepts included information related to a number of conditions of approval, such as providing data on its Postmarket study and including a patient quality of life question in that study. In 2000, the sponsor did not comply with the condition of approval to separate data by patients' clinical histories, but did complete this in its 2004 annual report. Therefore, in 2004, TMJ Concepts addressed all conditions of approval except one – submitting annual reports each year. Although all conditions of approval were not met and FDA was not able to review 5 years of annual reports, FDA found that the 2000 and 2004 annual reports provided adequate data and no additional information was required of the sponsor for those two reports.

TMJ Implants, Inc.

- The GAO found the sponsor combined data on five different device components, making it impossible to judge the safety or efficacy of several of its devices under review. Compounding the inadequacy of the company's application were disagreements within FDA between staff reviewers of the data and agency managers who decide on approval. In the end, management conceded that staff had raised legitimate concerns, but determined that the need for the devices outweighed the concerns. A senior FDA manager broke the logjam and intervened with a new policy review standard declaring surgeons and their patients share FDA's risk responsibility. Ultimately, all TMJ Implants, Inc. devices were approved.¹⁹
- The GAO investigation further found that TMJ Implants, Inc. had submitted several annual reports for both of its devices under review that lacked sufficient information regarding patient follow-up. FDA said the sponsor also underreported problems experienced by patients—known as adverse events—associated with the devices. FDA issued letters to the sponsor asking it to resolve these concerns, yet the sponsor repeatedly provided inadequate responses. This situation ultimately led FDA to file an administrative complaint for civil monetary penalties against the sponsor, which resulted in a decision from an administrative law judge in favor of FDA on July 6, 2007.¹⁹ In October 2009 the United States Court of Appeals Tenth Circuit ruled in favor of the FDA in a civil money penalties case against TMJ implant device manufacturer, TMJ Implants, Inc. and President, Dr. Robert W. Christensen, for failure to submit 17 medical device reports and was ordered to pay \$340,000 in civil penalties.²⁰ TMJ Implants Inc. declared bankruptcy in 2010 and the company was subsequently sold to Croker Ventures. TMJ Implants, Inc. devices will now be marketed under the name TMJ Medical.
- Information revealed during the 1999 Dental Products Panel meeting indicated that TMJ Implants, Inc. received 361 MDR reports, but determined that only four were device-related and reportable to the FDA.²¹ Surgeons and patients were blamed for the remaining failures.
- In its approval of TMJ Implants, Inc. devices, FDA management acknowledged that there were concerns about the quality and quantity of clinical data provided by the sponsor.

However, FDA management dismissed this stating that the clinical data were not to be expected of high quality because the sponsor was a small manufacturer. It then decided that either good engineering data or good clinical data was acceptable to approve a device—not necessarily both—and that it deemed the engineering data for the TMJ Implants, Inc. total joint implant to be satisfactory though even some engineering concerns had not been addressed.¹⁹

- Upon approval of the TMJ Implants, Inc. partial implant, two FDA staff wrote “respectful disagreement” memos. One indicated that the conditions of approval did not mitigate the concerns she highlighted in her memo.¹⁹
- The TMJ Association twice filed petitions with the FDA to hold an open hearing on its decision to approve the TMJ Implants, Inc. Fossa-Eminence Prosthesis after a Dental Products Panel concluded that not only were scientifically valid clinical studies to support the use of the device lacking, but also there were no clear indications for use. Further, clinical and/or testing data demonstrating the effect of the metal eminence on the natural mandibular condyle was not presented. The TMJ Association’s petitions were denied - twice.

The Biomet-Walter Lorenz Implant

- A Dental Products Panel meeting was held on August 22, 2002 to evaluate the Lorenz Surgical TMJ implant now being marketed as Biomet Microfixation. The Panel reviewed the data submitted from Biomet’s clinical study and unanimously approved the device. Two and one half weeks later, the FDA conducted an inspection at one of the two implanting surgeons’ institutions and found serious violations including:²²
 - Failure to obtain signed and dated informed consent documents from all study subjects prior to participation in the study.
 - Failure to conduct the study in accordance with the investigational plan.
 - Failure to maintain accurate, complete, and current subject records.
 - Failure to use the Institutional Review Board (IRB) approved informed consent form for all study subjects.

The result was that 40 of 180 cases had to be dropped from the study. When Dane Miller, President of Biomet was asked during the Dental Products Panel meeting why he brought the device to panel before the company reached their designated case number, he responded that the FDA had recently approved a device without data so he felt his company deserved equal treatment.

"There were a million red flags," said Mark Patters, DDS, who, between 1999 and 2002, served as an FDA advisory panel member for all four of the device hearings and who voted to approve three of them. "You don't have to know the particulars to know the science wasn't there."⁵

FDA Mechanisms for Oversight of Medical Devices

TMJ device history at the FDA can be reduced to two words—no science. Every TMJ device was approved with blatant lack of scientific evidence of safety and efficacy. Indeed, at the very outset when a manufacturer submits a PMA for a medical device, the FDA should evaluate the quality of the scientific and bioengineering data and reject the application if the data are flawed. It is advisable that prior to approving a device, FDA should inspect facilities to ensure that clinical studies are carried out according to established rules and regulations.

What follows is an account of the mechanisms FDA employs in conducting device oversight: The Association describes what went wrong in the past with TMJ devices and what we recommend for remedying the situation in the future.

Classification

The FDA classifies devices according to level of control necessary to assure the device's safety and effectiveness and the degree of risk to the patient or user. Class I devices pose the least risk; Class III the most. Class III devices impose the most stringent regulations on the manufacturer. When The TMJ Association spoke with FDA staff in 1992, the Association was told that TMJ implants "fell through the cracks" and had been omitted from dental devices considered for classification during Dental Products Panel Meetings in 1987 and again in 1989. According to Public Citizen, "At the very least, it would have been prudent for FDA to call for safety and effectiveness data from all TMJ implant manufacturers" when problems first surfaced with the Vitek devices and at least by 1987.²³ During the June 1992 Congressional Hearing, *Are FDA and NIH Ignoring the Dangers of TMJ (Jaw) Implants?*, Mr. Benson, then Director of the Center for Devices and Radiological Health (CDRH) was asked when the FDA was going to classify TMJ devices. Mr. Benson replied, as soon as possible.²⁴ At a February 1993 meeting, the FDA Dental Products Panel did finally recommend that TMJ devices be placed in Class III but there were errors in filing. The result was that PMAs from the manufacturers were not requested until 1999 – six years later. TMJ devices are now classified as Class III. Given this dilatory performance, it is essential that FDA address future classifications of all medical devices according to the appropriate level of control and in a timely manner.

Device Tracking

The FDA requires manufacturers to track certain devices upon order from the agency. Tracking is intended to facilitate notification and recall in the event a device presents a serious risk to health that requires prompt attention. Temporomandibular Joint (TMJ) prostheses, glenoid fossa prostheses, and mandibular condyle prostheses are among devices that the FDA has ordered manufacturers to track. But many patients have told The TMJ Association that they had never been contacted by the manufacturer of their device in an attempt to keep the patients' contact information current. Moreover, when the TMJ Association asked FDA staff if assessing compliance of the tracking system was part of the FDA inspection process, the reply was no. **The FDA should include in their inspection process evidence that the manufacturer is complying with a device-tracking order.**

MedWatch

MedWatch is a voluntarily reporting system in which either professionals or the public can report a serious adverse event from a medical device, drug, biologic, dietary supplement or cosmetic. In 1986, the FDA was informed of adverse problems related to the Vitek implant, but due to problems with their Medical Device Report (MDR) program, the reports were dismissed. Over the years MedWatch reports have been filed on all TMJ devices. In July 2010 The TMJ Association asked FDA officials how many reports had to be filed before FDA took action, since in addition to those submitted by the association there were many others submitted by individual patients. We asked the FDA to review all MedWatch reports on TMJ devices over the years. Responding to The TMJ Association's request, FDA analyzed TMJ implant-related adverse

event reports submitted between April 30, 2004 and Aug. 17, 2010. The analysis found 52 percent of TMJ patients had implants replaced within three years or less after implantation because of extreme pain. This is considerably shorter than the expected minimum five-year life span of the device, based on premarket mechanical testing. What is important to note is that this analysis was conducted only after The TMJ Association pointed out the problems it was hearing from patients to the FDA. **The current ineffective MedWatch and Medical Device Reporting systems must be drastically improved if the agency is to respond to a medical device problem effectively and promptly to save lives. Further the agency should conduct an awareness campaign directed toward health professionals and the public to alert them to the importance of these systems and their role in reporting device-related problems.**

Recalls

The FDA became the responsible party to conduct the Class I Recall of the TMJ Vitek implant. The FDA was ill prepared to carry out that recall. **If a company does not take the responsibility to carry out an FDA recall, a system should be in place so that the FDA can respond in an efficient and timely manner.**

The Plight of the Patient: The Economic Cost

When a patient receives an implant, there is no warranty comparable to those accompanying the purchase of consumer goods or appliances. If the device needs to be explanted within a short period of time (as happened recently in the case of 52 percent of TMJ implant patients whose devices had to be removed in under three years' time), the patient does not get a replacement implant free of charge, nor will the surgeon or hospital provide free services. Further, no one will compensate the patient for time lost from work. Responsibility rests solely with the patient to pay for the next, or 8th or 32nd procedure.

In the case of failure of a TMJ total joint implant, it is all but guaranteed that another implant will be needed to provide jaw function, albeit that function may be limited because of pain and muscle atrophy. Two surgical procedures will be necessary: one to remove the failed implant and a second to implant a customized new device. Following the explantation of the failed device a CT scan is necessary so that the custom device will accommodate the jaw anatomy. The typical costs, based on 2010 figures, are \$30,000 for a pair of devices, \$50,000 for surgical fees and \$75,000 for hospital costs: a total between \$150,000 and \$175,000. Insurance coverage for TMJ disorders is uncertain and surgeons typically expect a sizable amount of their fee to be paid in advance. We don't have data on the out-of-pocket costs, such as, for medications; travel to and from treatment facilities, lost time from work, childcare, surgical and medical complications, an implant patient absorbs. If the life span of a TMJ device is five years and a patient is 30 years old, he or she can expect to have 10 more device procedures by the age of 70. The financial impact on the patient and their loved ones is enormous. Obviously, many patients lose their jobs and are no longer able to work. Their spouses may also lose their jobs because of the impact on the employed person's company insurance. In order to continue TMJ care, treatment and future surgeries, many families declare bankruptcy, patients and their spouses divorce so that the patient can receive Medicaid or Medicare, parents deplete their retirement investments paying for their child's care and parents deplete the college funds of their children. These are just some of the ways patients are affected and deal with the financial strains of an implant gone awry.

What is obvious is that the financial costs are borne not just by the patient and their loved ones but by society at large.

The Plight of the Patient: The Physical and Medical Costs

At a time when the miracles of medical devices are touted to the public, it is important that the problems patients face when implants fail are also reported. The following lists are compiled from information contained in The TMJ Association's implant patient files —information that patients relayed to us in letters, e-mails, phone calls or in person.

Device-Related Problems

- Broken screws
- Device slipping, squeaking, popping or bulging out the side of the face
- Device material particulated and/or splintered becoming embedded into surrounding tissue and migrated.
- Fractured fossa component
- Fractured mandibular/condylar component
- Harvested material necrosed, particulated and migrated
- Implant perforated the skull, ear or face
- Screws loose

Adverse Surgical Events

- Cardiovascular events
- Death
- Paralysis (facial)
- Stroke
- Transient Ischemic attack
- Traumatic Brain Injury
- Trigeminal Nerve damage

Post-Implant Complications

- Allergic reactions – hives, rashes, itching, asthma
- Bone degeneration
- Burning, ice-pick like pain in joint area
- Change in bite, necessitating orthodontics or other dental procedures.
- Decreased Range of jaw motion
- Device material leached into surrounding tissues or into the blood stream
- Facial deformity
- Foreign body giant cell reaction
- Harvest site (buttocks, abdomen, rib, ear cartilage, muscle, rib) complications and pain at harvest site.
- Heterotopic bone growth – ankylosis necessitating a surgical procedure to debride the area.
- Infections that were not responsive to antibiotics and necessitated explantation, flap back face skin and “power wash” the skull with antibiotics
- Lymphadenopathy
- Metal toxicity

- Metallic taste in the mouth
- Metallosis
- Micro-particles of material migrated throughout tissues.
- Skin discoloration, frostbite on skin over implant in cold weather
- Swelling that does not subside
- Teeth broken during surgical procedure

Systemic Problems/Other Medical Conditions Following Implant Surgery

- Abnormal thyroid function
- Bladder dysfunction
- Chronic Fatigue Syndrome
- Chronic respiratory, urinary tract, pelvic, or gastrointestinal infections
- Chronic headaches
- Cognitive dysfunction
- Cold extremities
- Constant low-grade fever
- Dizziness, balance issues
- Drooling
- Dystonic tremor
- Ear pain, diminished or hearing loss, hyperacusis
- Eye lid paralysis necessitating gold leaf implant or suturing eye lids together
- Face unrecognizable after surgery
- Fibromyalgia, Myofascial Pain Dysfunction
- Facial Paralysis
- Flu-like symptoms
- Headaches
- Hoarseness
- Intolerance to heat and/or cold
- Memory problems
- Muscle atrophy
- Muscle spasms
- Night sweats
- Numbness
- Parotid Gland Cysts, stones
- Post-traumatic Stress Syndrome
- Seizures
- Sjogren's Syndrome
- Sleep apnea or sleep disorders
- Snow blindness, blurred vision, dyslexia
- Speech difficulty
- Stroke
- Swallowing Difficulties
- Teeth breaking gradually following procedure

The Need for More Research

Temporomandibular Disorders are still a poorly understood condition. However, recent studies confirm that co-morbidities exist with TMD and research has stimulated investigation into what may be the common underlying mechanisms for these conditions. Some of these conditions are included among the above. However, it may be the case that implant procedures or the materials used in TMJ devices trigger or increase the risk of these other conditions and patients might not develop them in the absence of surgery and/or implants. It is also possible that some of these symptoms are totally unrelated to TMJ implants, and are either a component of the TMJ complex disorder, or a manifestation of an entirely different disease. But, we will not know the answers until studies are conducted. Another area of interest is the sex difference. Ninety percent of the most severely affected are women of childbearing age. The FDA has an interest in whether men and women may respond differently to certain medical devices and the procedures in which they are used. Several FDA studies have focused on identifying some of these differences. Studies in collaboration with the NIH would no doubt yield valuable information on Temporomandibular Disorders as well as differential systemic effects of TMJ implants depending on the sex of the patient.

The Quagmire

TMJ implant patients live in a world of emotional blackmail. If they complain to the FDA, their surgeon will no longer provide pain medication or support their disability claims. If they complain about their device to the surgeon, their concerns may be dismissed, the patient blamed and they may be told to see another surgeon. It is not unusual for patients either to be abandoned because of attitudes or to abandon their surgeon because of insensitivity or denial of their problems. So the patient may find another surgeon who will explant the failing device and implant another. Meanwhile, the original surgeon believes that the patient is doing well and calls the surgery a success because the patient never returned. The second surgeon will not report the explantation of the original device either to the manufacturer or the FDA. In many instances the problems the patients are having are not brought to the attention of the manufacturers by the surgeons. What we have witnessed over a half century is a quagmire. The manufacturer blames the surgeons and patients for the device failure. The FDA says it did its job. The surgeons blame the FDA and the patients, saying they thought the FDA had the data or the patient must have done something wrong to cause the problems. And this "whose on first" continues and it is tragic, not funny. It is clear that in the silo system we have now no one has to accept responsibility or be accountable to the patient.²⁵

The Future of TMJ Devices: A Paradigm Shift

On February 7, 2011 the FDA ordered the manufacturers of TMJ implant devices to conduct Post-market Surveillance studies and to submit protocols within 30 days. A few days after the order was issued, The TMJ Association received a question from a TMJ patient, "Why should we believe the data the manufacturers will present when we were led to believe they had scientific data 10 years ago?" That question provoked much thought and discussion within The TMJ Association, which led us to the conclusion that we could no longer accept the status quo for TMJ patients.

A TMJ Device Round Table

As a patient advocacy organization a frustration over the years has been the lack of cooperation and collaboration among the major interested parties. As we viewed the recent directive from the FDA we saw an opportunity for a major paradigm shift. We would propose a formal agreement to work together to ensure that the best clinical and bioengineering science, based upon robust scientific principles and good manufacturing practices, will be directed toward the implant patients and their devices. Collaboration would take the form of a TMJ Device Round Table where all stakeholders could come together to discuss how to build a body of data on implant performance, patient satisfaction, side effects and complications—data which could better guide patients' health care decisions as well as future device designs to yield optimal patient outcomes."²⁶ The Round Table will include manufacturers, bioengineers, clinical, basic, and bioengineering scientists, representatives from FDA and NIH, surgeons, registry experts, and The TMJ Association. On March 9, 2011 we presented our concept to the CDRH Director, Dr. Jeffrey Shuren and staff. They responded with enthusiastic support and intent to participate. The manufacturers have also been positive in their response. We look forward to the challenges of this new approach and are optimistic that results will benefit all stakeholders, especially TMJ patients.

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Summary and Recommendations for Reform of the Device Approval Process

The statement of The TMJ Association documents in detail the past failings of device manufacturers, health professionals, and the Food and Drug Administration at all stages of the device approval and monitoring process—from design and manufacture through safety and efficacy testing and post-market surveillance, and even in recalls. The result has been a human disaster affecting thousands of patients who have been harmed physically, emotionally, and financially—individuals who are now worse off in the severity of their pain and jaw dysfunction as well as suffering serious systemic complications, even death.

FDA – Transparency and Communication

The convening of a hearing to examine the device approval process and propose reforms comes at a time of change within the FDA, which augers well for the future. Over the past decade The TMJ Association made several unsuccessful attempts to meet with the Director of the Center for Devices and Radiological Health (CDRH) to discuss TMJ issues. All the more reason, then, that we applaud Dr. Shuren's eagerness to hear from all stakeholders in the device arena. Several weeks after Dr. Shuren assumed that Directorship, I, as President of The TMJ Association, was invited to participate in a conference call with him and other advocates to discuss our concerns with the Center. Several other conference calls followed. On July 10, 2010, I asked to meet with Dr. Shuren. He immediately responded and accommodated my scheduled visit to Washington. Since he became CDRH director he has held Town Hall meetings throughout the country at which patients have had a voice. However, the challenge for FDA is to give equal voice and participation to all stakeholders. For example, last year I watched the Institute of Medicine meeting webcast on the 510K process. In the room were 399 representatives of the device industry and one representative of the consumer. In a letter to Dr. Shuren I asked him to "please remember we are greatly outnumbered and greatly outspent by those who have the most to gain financially from devices." Yet it is we the patients who have the most to gain or lose from devices—our quality of life, even our lives.

The Future of TMJ Devices: A Paradigm Shift

On February 7, 2011 the FDA ordered the manufacturers of TMJ implant devices to conduct Postmarket Surveillance studies and to submit protocols within 30 days. A few days after the order was issued, The TMJ Association received a question from a patient, "Why should we believe the data the manufacturers will present when we were led to believe they had scientific data 10 years ago?" That question provoked much thought and discussion within The TMJ Association, which led us to the conclusion that we could no longer accept the status quo for TMJ patients. As we viewed the recent directive from the FDA we saw an opportunity for a major paradigm shift. We would propose a formal agreement to work together with all interested parties to ensure that the best clinical and bioengineering science, based upon robust scientific principles and good manufacturing practices, will be directed toward the implant patients and their devices. Collaboration would take the form of a **TMJ Device Round Table** where all stakeholders could come

together to discuss how to build a body of data on implant performance, patient satisfaction, side effects and complications—data which could better guide patients' health care decisions as well as future device designs to yield optimal patient outcomes."²⁵ The Round Table will include manufacturers, bioengineers, clinical, basic, and bioengineering scientists, representatives from FDA and NIH, surgeons, registry experts, and The TMJ Association. On March 9, 2011 we presented our concept to Dr. Shuren and his staff. They responded with enthusiastic support and intent to participate. The manufacturers have also been positive in their response. We look forward to the challenges of this new approach and are optimistic that results will benefit all stakeholders, especially TMJ patients.

* * *

The TMJ Association submits the following recommendations to reform the Medical Device Approval Process:

Rec. 1: Review the classification process for all medical devices to assure that the classification is conducted in a timely manner and reflects the degree of harm that can result from device failure.

Rec. 2: Establish a TMJ Implant Registry.

A medical implant registry should be mandatory, independently monitored, include representation by all stakeholders, and include a process for device retrieval and analysis. It should be internationally compatible. Data analysis should enable detection of problems in time to minimize the number of people who could be damaged by the device and thus prevent future suffering and save lives. The registry would also be a means of assessing the success rates for implants and glean information on the scale of device problems from minor to major.

Rec. 3: Assure FDA Monitoring of Postmarket Surveillance.

If a device manufacturer is ordered to continue a clinical study following approval, it is FDA's obligation to see to it that the study is being conducted appropriately, and that the required reports are received by FDA on schedule.

Rec. 4: The FDA should have mechanisms in place to assure that manufacturers comply with device-tracking requirements.

The Food and Drug Administration requires manufacturers to track certain devices upon order from the agency. Tracking is intended to facilitate notification and recall in the event a device presents a serious health risk to the patient health that requires prompt attention. Temporomandibular Joint (TMJ) prostheses, glenoid fossa prostheses, and mandibular condyle prostheses are among devices that the FDA has ordered manufacturers to track. But many patients have told The TMJ Association that they had never been contacted by the manufacturer of their device in an attempt to keep the patients' contact information current. Moreover, when the TMJ Association asked FDA staff if assessing compliance of the tracking system was part of the FDA inspection process, the reply was no.

Rec. 5: If a company is unable to fulfill its responsibilities in the event of a recall of one its products, a system should be in place allowing FDA to conduct the recall promptly and efficiently.

The FDA became the responsible party to conduct the Class I Recall of the TMJ Vitek implant but was ill prepared to carry out that recall.

Rec. 6: The MedWatch and Medical Device Reporting systems must be improved. The FDA should conduct an awareness campaign to educate health professionals and the public of the importance of reporting device-related adverse events to the agency.

MedWatch is a voluntary reporting system in which professionals and the public can report a serious adverse event from a medical device, drug, biologic, dietary supplement or cosmetic. In 1986, the FDA was informed of adverse problems related to the Vitek implant but because of problems with the Medical Device Report (MDR) program, the reports were dismissed. Over the years MedWatch reports have been filed on all TMJ devices. In July 2010 The TMJ Association asked FDA officials how many reports had to be filed before FDA took action, since in addition to those submitted by the Association there were many others submitted by individual patients. We asked the FDA to review all MedWatch reports on TMJ devices over the years. Responding to The TMJ Association's request, FDA analyzed TMJ implant-related adverse event reports submitted between April 30, 2004 and Aug. 17, 2010. The analysis found 52 percent of TMJ patients had their implants removed three years or less after surgery because of extreme pain. This is considerably shorter than the expected minimum five-year life span of the device, based on premarket mechanical testing. What is important to note is that this analysis was conducted only *after* The TMJ Association pointed out the problems to the FDA.

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SOFTWARE ISSUES FOR
THE MEDICAL DEVICE APPROVAL PROCESS

SUBMITTED TO THE
SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE
HEARING ON

A DELICATE BALANCE: FDA AND THE REFORM OF THE
MEDICAL DEVICE APPROVAL PROCESS

WEDNESDAY, APRIL 13, 2011

Introduction

Chairman Kohl, Ranking Member Corker, and the distinguished members of the Special Committee on Aging, I would like to thank you for the invitation to submit a statement for the record regarding the impact of software-related issues on reform of the medical device approval process. My comments below are based on work supported in part by the Institute of Medicine, a Sloan Research Fellowship, the National Science Foundation Directorate for Computer and Information Science and Engineering, and the Office of the National Coordinator for Health Information Technology. However, all opinions, findings, and conclusions are my own and do not necessarily reflect the views of the IOM, Sloan Foundation, NSF, ONC, or my past or present employers.

My name is Kevin Fu. I am a faculty member in Computer Science at the University of Massachusetts Amherst where my research pertains to trustworthy computing for medical devices. I have interacted several times with FDA with multiple presentations on medical device software at FDA's Center for Devices and Radiological Health. My educational qualifications include a Ph.D., master's degree, and bachelor's degree from M.I.T.'s Department of Electrical Engineering and Computer Science. My industrial experience in software systems includes past employment at Cisco Systems, Microsoft, Hewlett-Packard, and the Information Systems department at Holland Community Hospital. In my nearly two decades of experience in software related to health care, I have observed both the risks and benefits of software for medical devices. Highlights include participation in the roll out of a hospital information system to improve patient care at a community hospital and the security analysis of a medical device showing that an implantable cardiac defibrillator could be wirelessly tricked into inducing a fatal heart rhythm.

I attach for the record my presentation and report on *Trustworthy Medical Device Software* commissioned by the Institute of Medicine at the National Academies for the "Public Health Effectiveness of the FDA 510(k) Clearance Process" committee, which will shortly render its recommendations to FDA. My statement summarizes these findings and suggests several questions to ask about the role of software in the medical device approval process.

Findings on Software Issues for Medical Devices

Despite the lessons learned by tragic accidents, such as the radiation injuries and deaths caused by the Therac-25 linear accelerator two decades ago (Leveson, 1993), medical devices that depend on software continue to injure or kill patients in preventable ways. Problems in medical device software result largely from a failure to apply well-known systems engineering techniques, especially during specification of requirements and analysis of human factors. Problems ranging from poor user interfaces to overconfidence in software have led to accidents such as fatally incorrect dosages on infusion pumps and in radiation therapy. A common trait for adverse events in medical device software is that the problems are often set in place before any implementation begins.

Illustrative Examples to Motivate Software Questions

Insufficient number of software experts at FDA. It was explained to me by a former FDA CDRH director that seldom does an FDA inspector assigned to review a 510(k) application have experience in software engineering—even though the majority of medical devices today rely on software. Over half the medical devices on the US market now involve software (Faris, 2006).

Opting to forgo a wireless pacemaker. Karen Sandler, General Counsel for the Software Freedom Law Center, was concerned about the safety of her software-controlled pacemaker because it would have a long-range, wireless interface¹. She selected an older pacemaker without a wireless component:

I [was prescribed] a pacemaker. My first question was, "Could I take a look at the [computer] code?" I offered to sign an NDA.... No one would take this concern seriously. I was at risk of sudden cardiac death.

...

After talking to many doctors who didn't really understand why I would be concerned about the safety of the software of the device, finally I found a doctor....who [suggested], "What if we find you an old device without a wireless component?"

Personally, if I were prescribed a medical device by a well informed physician, I would accept the device for my health. However, with increased software complexity, patients and physicians cannot make informed decisions without access to better information about software risks.

Malware on medical devices. An Information Technology (IT) professional from a VA medical center sought my advice at the RSA Security Conference on how to recover from malware that had infected her hospital computer systems. She explained that her medical systems were routinely infected with malicious software because health care professionals like to check email on the same machines used for patient care. However, email is just one potential vector for malware to infect medical devices. Medical devices are exposed to persistent software-based threats when pathways exist to the Internet. I asked why not have separate computers, and she replied that there was not enough desk space. I asked if any of the computers were connected to radiation-emitting machines, and she declined to comment.

¹<http://www.usenix.org/events/healthsec10/tech/>

Severe underreporting. Users are not incentivized to report software security problems. At the USENIX Workshop on Health Security and Privacy¹, John F. Murray Jr. (Software Compliance Expert, FDA CDRH/Office of Compliance) speaking for himself commented that:

We actually know that cybersecurity and viruses are huge problems for medical devices—for networked medical devices. We know that because I get phone calls all the time. We know that because people complain all the time. But unfortunately, the users aren't complaining in any formalized way.

...

If you [discover] some problems, some issues, you need to get into the mode of reporting these kinds of issues. And making it known to the FDA and the authorities that this is a really big issue. Now this is going to become extremely—a hundred times more important when we start using electronic health records.

...

What does the law require you to report? If you're a user facility, the law requires you to report any deaths involving medical devices, or any serious injuries involving medical devices. These things have actually had to occur [to require reporting].

Scott Bolte of GE Healthcare emphasizes that for security problems, formal reporting is especially lacking². This advice was given to FDA six years ago:

Although there is a lot of anecdotal evidence that malicious software has compromised medical devices, there is a notable lack of formal evidence. So without this formal reporting, the FDA is limited in its ability to act or intervene. Reporting is something providers and arguably the manufacturers themselves can and should start doing immediately.

Inconsistency within FDA on substantial equivalence. At the IOM workshops on the 510(k) clearance process, former FDA officials presented contradictory advice on "substantial equivalence." This concept is important because a manufacturer that demonstrates substantial equivalence to an old predicate device may choose a less thorough regulatory pathway for clearance of a new device.

Dr. Christy Foreman's presentation³ includes a flowchart that effectively asks, "Does the new technical characteristics raise new types of safety or effectiveness questions." My examples in this section should demonstrate that medical device software can raise new types of safety or effectiveness questions.

However, the slides from Heather Rosencrans (former Director, 510(k) Staff, Office of Device Evaluation, FDA CRDH) seem to indicate that there is never a reason to question the substantial equivalence of a new digital control linked with a previous analog control as a predicate³. Then Dr. David Feigel (former Director, CDRH) said during a June 14, 2010 IOM workshop that:

One of the interesting classes is radiation equipment...even the software, which I wonder where they got the first predicate for software.

-David Feigel, Fmr. Director, FDA CDRH

²<http://www.fda.gov/MedicalDevices/Safety/MedSunMedicalProductSafetyNetwork/ucm127816.htm>

³IOM Workshop on Public Health Effectiveness of the FDA 510(k) Clearance Process, March 1, 2010.

The misconception that software poses risks no different from hardware is illustrated by the tragedies of the Therac-25 (Leveson, 1993), a radiation-emitting device that modified its systems to rely on digital software controls rather than analog hardware controls in the 1980s. This change combined with other human elements raised new safety risks and ultimately injured and killed a number of patients. Unlike a mechanical component, software is not exhaustively testable or interpolatable. In the case of the Therac-25, one result of this software issue was improper switching between therapies that resulted in massive radiation overdoses. Massive overdoses on software-controlled, radiation-emitting machines continue to happen today (Bogdanich, 2010).

Questions

Based on the examples above, I suggest several questions for the Committee to consider.

1. Questions on reporting and statistics
 - (a) How many cleared and approved medical devices currently use radio communication (e.g., wireless, MICS)?
 - (b) What percentage of medical devices currently cleared or approved involve software, radio or wireless communication, or Internet connectivity?
 - (c) What percentage of medical device applications currently under review involve software, radio or wireless communication, or Internet connectivity? To what degree is this amount increasing or decreasing?
 - (d) To what degree are critical device functions being performed by software (vs. hardware)? Is the amount increasing? Decreasing?
2. Questions on risk/benefit analysis
 - (a) How does a manufacturer demonstrate that wireless communication or Internet connectivity leads to overall better patient outcomes?
 - (b) How does a patient or physician learn what programming languages were used in the creation of medical device software? Different programming languages carry different risks.
 - (c) What effect does software have on reliability? Availability? Maintainability? Ease of use?
 - (d) How do these software characteristics compare with similar implementations in hardware? Does the software make the device safer or more effective?

3. Questions on substantial equivalence

- (a) Why do past senior administrators in CDRH have conflicting definitions of what it means for software-based medical devices to have “substantial equivalence to a predicate” in the context of the 510(k) process? Some claim perhaps unintentionally that software and hardware are no different. On the other hand, some have stated that they do not know how any software could be substantially equivalent to a hardware-based predicate. What is FDA CDRH's current position and how does CDRH plan to develop a more consistent definition across all its scientists and engineers?
- (b) What does data from the predicate device reveal about the new device? Does predicate data save time in specification of the new device? Does predicate data save time in testing of the new device?

4. Question on informed consent for disclosing risks to patients

What are manufacturers required to disclose to physicians about medical device software risks? How does the process differ for devices that are higher risk or consequence?

5. Questions on security of medical device software

- (a) To what extent will existing recall processes be effective against zero-day software vulnerabilities⁴?
- (b) What contingency plans are in place should the software equivalent of the 1982 Chicago Tylenol cyanide poisonings take place? How much time would it take a manufacturer to address a software vulnerability?
- (c) How does FDA balance the benefits of software with the risks of low-probability, high-consequence problems in software that may result in significant injuries or deaths?

6. Questions on education and FDA personnel

- (a) What is the recommended training for health care professionals for reporting software problems? Which hospital administrator is responsible for this reporting, and how are they incentivized to look for potential problems? That is, who takes ownership of the risks?
- (b) What special training do FDA reviewers receive specific to software engineering, requirements specification, system engineering, hazard analysis, dependable computing, and trustworthy computing?
- (c) Why are there no software experts among any of the past fellows of the FDA Commissioner's Fellowship Program?
- (d) What does FDA do to attract and retain top talent for handling software issues? What employers are the prime competitors for talent?

⁴A zero-day vulnerability is a security problem where the time between discovery of the flaw and exploitation of the flaw is less than a day.

Recommendations

Recommendations to increase the trustworthiness of medical device software include (1) regulatory policies that specify outcome measures rather than technology, (2) collection of statistics on the role of software in medical devices, (3) establishment of open-research platforms for innovation, (4) clearer roles and responsibility for the shared burden of software, (5) clarification of the meaning of substantial equivalence for software, and (6) an increase in Food and Drug Administration (FDA) access to outside experts in software.

Conclusion

There is no question that software provides significant benefits for the function of medical devices. However, software also presents risks qualitatively different from risks of hardware and mechanical components. Many risks of medical device software could be mitigated by applying well-known systems engineering techniques, especially during specification of requirements and analysis of human factors.

Today, the frequency of news reports on tragic, preventable accidents involving software-based medical devices falls somewhere between that of automobile accidents and airplane accidents. Event reporting on tragic medical device accidents is likely headed toward the frequency of the former given the continued increase in system complexity of medical device software and present-day regulatory policies that do not adequately encourage use of modern software engineering and system engineering practices. Left unbalanced, poorly engineered software may become the O-ring of medical devices.

I hope that my statement provides helpful context for the Committee to ask important questions such that FDA can better balance the risks and benefits of medical device software.

Trustworthy Medical Device Software

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Abstract

This report summarizes what the computing research community knows about the role of trustworthy software for safety and effectiveness of medical devices. Research shows that problems in medical device software result largely from a failure to apply well-known systems engineering techniques, especially during specification of requirements and analysis of human factors. Recommendations to increase the trustworthiness of medical device software include (1) regulatory policies that specify outcome measures rather than technology, (2) collection of statistics on the role of software in medical devices, (3) establishment of open-research platforms for innovation, (4) clearer roles and responsibility for the shared burden of software, (5) clarification of the meaning of substantial equivalence for software, and (6) an increase in FDA's access to outside experts in software. This report draws upon material from research in software engineering and trustworthy computing, public FDA data, and accident reports to provide a high-level understanding of the issues surrounding the risks and benefits of medical device software.

1 Introduction

Software plays a significant and increasing role in the critical functions of medical devices. From 2002–2010, software-based medical devices resulted in over 537 recalls affecting more than 1,527,311 devices¹ [49]. From 1999–2005, the number of recalls affecting devices containing software more than doubled from 118 to 273 [2]. During this period, 11.3% of all recalls were attributable to software failures. This recall rate is nearly double compared to the period of 1983–1997 where only 6% of recalls were attributable to computer software [54]. For pacemakers and implantable cardioverter defibrillators, the number of devices recalled due to software abnormalities more than doubled from 1991–2000 [34]. In 2006, Faris noted the milestone that over half of the medical devices on the U.S. market now involve software [11].

Yet, despite the lessons learned by tragic accidents such as the radiation injuries and deaths caused by the Therac-25 linear accelerator over twenty years ago [29], medical devices that depend on software continue to injure or kill patients in preventable ways. Problems in medical

¹The total number of devices was computed by summing up the number of devices listed for each of the 537 FDA recalls attributed to software. A device subject to multiple recalls would be counted once per recall.

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Sidebar 1: The many definitions of trustworthiness.

One definition of *trustworthy software* is "software that is dependable (including but not limited to reliability, safety, security, availability, and maintainability) and customer-responsive. It can fulfill customer trust and meet the customer's stated, unstated, and even unanticipated needs [23]." Another definition emphasizes the multi-dimensional, system-oriented nature that trustworthiness of a system implies that it is worthy of being trusted to satisfy its specified requirements (e.g., safety, effectiveness, dependability, reliability, security, privacy) with some [quantifiable] measures of assurance [37]. The National Science Foundation associates trustworthiness with properties of security, reliability, privacy, and usability—arguing that these "properties will lead to the levels of availability, dependability, confidentiality and manageability that our systems, software and services must achieve in order to overcome the lack of trust people currently feel about computing and what computing enables [40]."

device software result largely from a failure to apply well-known systems engineering techniques, especially during specification of requirements and analysis of human factors.

"The ability of software to implement complex functionality that cannot be implemented at reasonable cost in hardware makes new kinds of medical devices possible.... [10]"

Software can help and hurt. Software can significantly affect patient safety in both positive and negative ways. Software helps to automatically detect dangerous glucose levels that could be fatal for a person using an insulin pump to treat diabetes. Medical linear accelerators use software to more precisely target the radiation dose. Remote monitoring of implanted devices may help to more quickly discover malfunctions and may lead to longer survival of patients [26]. However, medical device software contributes to the injury or death of patients. Problems ranging from poor user interfaces to overconfidence in software have led to accidents such as fatally incorrect dosages on infusion pumps [12, 16, 35] and radiation therapy [29, 4]. A common trait for adverse events in medical device software is that the problems are often set in place before any implementation begins (Table 1).

Medical devices ought to be trustworthy. In the context of software, trustworthiness is inextricably linked with safety and effectiveness. There are several definitions of *trustworthy software* (Sidebar 1) that vary by the specific contributions and terminology of various research subdisciplines. However, the fundamental idea is that software trustworthiness is a *system* property measuring how well a software system meets *requirements* such that *stakeholders* will *trust* in the operation of the system. The requirements include overlapping and sometimes competing notions of safety, effectiveness, usability, dependability, reliability, security, privacy, availability, and maintainability.

Failure to meaningfully specify requirements, complacency, and lack of care for human factors can erode trustworthiness. The lack of trustworthy medical device software leads to shortfalls in properties such as safety, effectiveness, usability, dependability, reliability, security, and privacy. Good systems engineering [46] and the adoption of modern software engineering techniques can mitigate many of the risks of medical device software. Such techniques include a technical and

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Eng. Stage	Adverse Event	Contributing Factor
Requirements Specification	Linear accelerator: Patients died from massive overdoses of radiation.	An FDA memo regarding the Corrective Action Plan (CAP) notes that, "Unfortunately, the AECL response also seems to point out an apparent lack of documentation on software specifications and a software test plan [30, p. 539]."
Design	Pacemakers/Implantable defibrillators: Implant can be wirelessly tricked into inducing a fatal heart rhythm [21].	Security and privacy need to be part of the early design process.
Human Factors	Infusion pump: Patients injured or killed by drug overdoses.	Software that did not prevent key bounce misinterpreted key presses of 20 mL as 200 mL [17].
Implementation	Infusion pump: Underdosed patient experienced increased intracranial pressure followed by brain death.	Buffer overflow (programming error) shut down pump [14].
Testing	Ambulance dispatch: Lost emergency calls.	An earlier system for the London Ambulance Service failed two major tests and was scuttled [20]. Ambulance workers later accused the computer system of losing calls and that "the number of deaths in north London became so acute that the computer system was withdrawn [53]." The ambulance company attributed the problems to "teething troubles" with a new computer system [53].
Maintenance	Health Information Technology (HIT) devices: Computers systems globally rendered unavailable.	An anti-virus update misclassified a core Windows operating system component as malware and quarantined the file, causing a continuous reboot cycle for any system that accepted the software update [32]. Numerous hospitals were affected. At Upstate University Hospital in New York, 2,500 of the 6,000 computers were affected [52]. In Rhode Island, a third of the hospitals were forced "to postpone elective surgeries and stop treating patients without traumas in emergency rooms [50]."

Table 1: Examples of adverse events where medical device software played a significant role.

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managerial mindset that focuses on “design and development of the overall system [30, p. 140]” as opposed to focusing on optimization of components; meaningful specification of requirements such as intent specifications [31]; application of systems safety [30], and static analysis [39].

Although it is possible to create trustworthy medical device software under somewhat artificial constraints to achieve safety and effectiveness without satisfying other properties, in practice it is difficult to find environments where the properties are not linked. A medical device that works effectively in isolation may lose the effectiveness property if another component engineered separately joins the system—causing unanticipated interactions. For example, a computer virus caused 300 patients to be turned away from radiation therapy because of shortfalls in security [38]. A security component can also reduce effectiveness if not designed in the context of system. For instance, a mammography imaging system may become ineffective if an automatic update of an anti-virus program designed to increase security causes the underlying operating system to instead fail [32].

Innovations that combine computer technology with medical devices could greatly improve the quality of health care [28, 39], but the same life-saving technology could reduce safety because of the challenges of creating trustworthy medical device software. For instance, an implantable medical device with no physical means to wirelessly communicate over long distances may work safely and effectively for years. However, adding remote monitoring of telemetry to the device introduces an interface that fundamentally changes the properties of the overall system. The new system must require not only that any component designed to interact with the device is trustworthy, but also that any component *capable of communicating with the device* is trustworthy.

2 Medical Devices, But with Software: What’s the Difference?

Patients benefit from software-based medical devices because “computers provide a level of power, speed, and control not otherwise possible [30].” Without computer software, it would not be feasible to innovate a closed-loop, glucose-sensing insulin pump; a remotely monitored, implantable cardiac defibrillator; or a linear accelerator that calculates the radiation dose based on a patient’s tissue density in each cross-section. However, the methodology used in practice to mitigate risks inherent to software have not kept pace with the deployment of software-based medical devices. For example, using techniques that work well to assure the safety and effectiveness of hardware or mechanical components will not mitigate the risks introduced by software. The following points use the writing of Pfleeger et al. [45] with permission. There are several reasons why software requires a different set of tools to assure safety and effectiveness.

- The discrete (as opposed to continuous) nature of software [43].

Software is sensitive to small errors. Most engineered systems have large tolerances for error. For example, a 1 inch nail manufactured to be 1.0001 inches or 0.9999 inches can still be useful. Manufacturing is a continuous process, and small errors lead to results essentially the same as the exact, desired result. However, consider a slight error in entering a bolus dosage on an infusion pump. A single key press error in selecting hours versus minutes could result in a bolus drip at 60 times the desired rate of drug delivery [13]. With some exceptions, small changes in continuous systems lead to small effects; small changes to discrete systems lead to large and often disastrous effects. The discrete nature of software also leads to limited ability to interpolate between test results. A system that correctly

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provides a radiation dose of 20 centigray (cGy) and 40 cGy does not in its own allow interpolation that it would work correctly for 32 cGy. There is also seldom no direct equivalent to "over-engineering" safety margins for software systems in comparison to physical systems.

- The immaturity of software combined with rapid change.

We keep running at an ever-faster pace to develop or use increasingly complex software systems that we do not fully understand, and we place such software in systems that are more and more critical. For example, a NITRD report from the High-Confidence Medical-Device Software and Systems (HCMDSS) Workshop [39] notes that:

"Many medical devices are, essentially, embedded systems. As such, software is often a fundamental, albeit not always obvious, part of a devices functionality. ... devices and systems are becoming increasingly complicated and interconnected. We may already have reached the point where testing as the primary means to gain confidence in a system is impractical or ineffective."

The recent reporting of several radiation deaths stemming from medical linear accelerators [3] further highlights how complexity outpaces the maturity of present-day practices for creating trustworthy medical device software:

"When it exceeds certain levels of complexity, there is not enough time and not enough resources to check the behavior of a complicated device to every possible, conceivable kind of input," said Dr. Williamson, the medical physicist from Virginia."

...

"But the technology introduces its own risks: it has created new avenues for error in software and operation, and those mistakes can be more difficult to detect. As a result, a single error that becomes embedded in a treatment plan can be repeated in multiple radiation sessions [3]."

Despite these challenges, software has improved the effectiveness of critical systems in contexts such as avionics. Modern airplanes would be difficult to fly without the assistance of software, but airplanes have also introduced safety risks of software by using fly-by-wire (electronic) controls instead of pneumatics. However, there is a substantial belief among software engineers that the medical device community (unlike the avionics community) does not take full advantage of well-known techniques for engineering software for critical systems. Many software engineers feel that that well-known technology not only lags, but is often ignored by medical device manufacturers. The safety culture of the avionics community does not appear to have a universal appreciation in the medical device community.

3 Techniques to Create Trustworthy Medical Device Software

While the role of software in medical devices continues to increase in significance, deployment lags for well-known techniques that can mitigate many of the risks introduced by software. The following discussion draws from several technical documents on software engineering for critical systems.

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The reader is strongly encouraged to read the full text of reports from NITRD on *High-Confidence Medical Devices* [39] and the National Academy on *Software for Dependable Systems* [10]. Highly recommended reading on software engineering for critical systems include *Safeware: System Safety and Computers* [30] and *Solid Software* [45] as well as evidence-based certification strategies such as the British Ministry of Defence Standard 00-56 [41].

3.1 Adopt Modern Software Engineering Techniques

Medical device software lags in the adoption of modern software engineering techniques ranging from requirements specification to verification techniques. Fortunately, mature technology is already available to address common problems in medical device software, and that technology has been successful in other safety-critical industries such as avionics.

Programming languages that do not support software fault detection as comprehensively as possible should be avoided in medical device software. The C programming language, for example, has a very weak type system, and so the considerable benefits of strong type checking are lost. By contrast, the Ada programming language provides extensive support for software fault detection. Similarly, mechanical review of software using a technique known as static analysis is a mature technology that can identify possible faults quickly and efficiently. Static analysis supports the overall goal of developing trustworthy software and should be employed to the extent possible. Type checking and static analysis are two mature methods that guide software engineers toward safer and more effective medical device software by reducing or eliminating common sources of software errors.

Some programming systems permit a specification of software to be embedded into the software itself so that compliance of the code with the specification can be checked mechanically. A commercial system that provides this capability along with commercial support of both the language itself and the associated static analysis tools is SPARK Ada. Techniques such as these should be employed whenever possible to enable more effective testing and analysis of software.

A software specification is a statement of what the software has to do. Stating precisely what software has to do has proven extremely difficult, and specification is known to be a major source of software faults. Research over many years has yielded formal languages, i.e., languages with semantics defined in mathematics, that can help to avoid specification errors. Formal specification has been shown to be effective, and formal specifications for medical devices should be employed whenever possible.

3.2 Meaningfully Specify Requirements

Safety failures in software tend to stem from flaws during specification of requirements [30, Ch. 15]. The first example from Table 1 represents a failure of requirements specification in a 1980s linear accelerator that killed a number of patients, and some believe that the lack of meaningful systems-level specification of requirements contributed to the deaths in the recent radiation overdoses from a modern linear accelerator [3].

In critical systems, meaningful specification of requirements is crucial to properly anchor testing and analysis. Shortfalls in specification of requirements will lead to a false sense of safety and effectiveness during subsequent design, implementation, testing, etc. An example of meaningful specification of a requirement might be "stop delivery if dose exceeds patient's prescription" or

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“patient’s received level of radiation must match level of radiation specified by operator.” Such specification of requirements go beyond purely functional descriptions such as “pressing start button begins primary infusion” or “delivered level of radiation adjusts to tissue density” that do not meaningfully capture the end-to-end system properties of a medical device.

Leading software engineers believe that many medical device manufacturers have an opportunity to significantly improve specification of requirements. In comparing medical devices to avionics systems, researchers wrote in the NITRD *High-Confidence Medical Devices: Cyber-Physical Systems for 21st century Health Care* report [39, p.59] that,

“Perhaps the most striking [difference] is the almost complete lack of regard, in the medical-device software domain, for the specification of requirements.”

A National Academy NRC report [10] similarly noted that,

“At least in comparison with other domains (such as medical devices), avionics software appears to have fared well inasmuch as major losses of life and severe injuries have been avoided.”

The NITRD report emphasizes that business models and incentives in the medical device sector lead to highly proprietary technologies that have two detrimental side effects: (1) companies are less likely to perceive value from specification of requirements, and (2) academic researchers have a much harder time participating in the innovation of medical device technology.

The NRC report recommended a direct path to dependable software [22] for critical systems such as found in medical devices. Under this philosophy, system designers focus on providing direct evidence to support claims about software dependability. The approach contrasts with prescriptive standards² that may otherwise dictate the specific claims. System designers are given flexibility to innovate by selecting the claims deemed necessary for the specific application at hand. Designers are forced to think carefully about proving the claims, but a difficulty remains in that the results are only as meaningful as the chosen claims.

3.3 Apply a System Engineering Approach

Software adds such complexity to the design of medical devices that the device must be treated as a system rather than an isolated component. The behavior of medical device software depends on its context within a system. Whereas biocompatibility of material may lend itself to conventional testing [27, Ch. 11], the complexity of software requires a systems engineering approach [46]. At a recent workshop on infusion pumps, it was pointed out that the 510(k) process is mostly a checklist, but this checklist approach provides less assurance as devices increase in complex system behavior [9]. Shuren provides an example of software-based medical devices that may operate safely and effectively in isolation, but not when integrated as a system [47]:

“Images produced by a CT scanner from one vendor were presented as a mirror image by another vendor’s picture archiving and communication system (PACS) web software. The PACS software vendor stipulates that something in the interface between the two products causes some images to be randomly ‘flipped’ when displayed.”

²IEC 62304 provides standards for development of medical device software, but not for the requirements themselves where many software flaws tend to begin [9].

The NITRD report from the High-Confidence Medical-Device Software and Systems (HCMDSS) Workshop [39] notes that:

“Integrating technology into the clinical environment—which includes practitioners, workflows, and specific devices—often lacks a holistic, systems perspective. Many medical devices are designed, developed, and marketed largely as individual systems or gadgets. Device integration, interoperability, and safety features are not considered during development, acquisition, or deployment.”

The rapid push toward device interoperability, wireless communication, and Internet connectivity will likely improve the effectiveness of care, but will also reinforce the notion of medical device software as systems rather than isolated devices. Because medical devices are no longer isolated devices, an effective strategy for increasing trustworthiness is to follow good system engineering methodology.

Evaluation of medical device software should require independent, third-party review by experts who are not connected with the manufacturer. Third party evaluation in combination with good systems engineering can mitigate many of the system-level risks of medical device software.

3.4 Mitigate Risks Due to Human Factors

Poor understanding of human factors can lead to the design of medical device software that reinforces risky behavior, which can result in injury or death. For instance, a software application card used in an implantable drug pump was recalled because of a user interface where the hours and minutes fields for a bolus rate were ambiguously labeled on the computer screen [12]. A patient with an implantable drug pump died from an overdose because the health care professional set the bolus interval to 20 minutes rather than 20 hours [13]. Thus, the drug was administered at 60 times the desired rate. The patient passed out while driving, experienced a motor vehicle accident, and later died after the family removed life support.

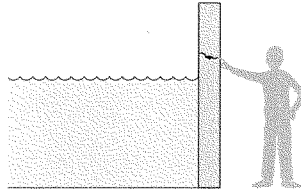
Unmitigated risks of human factors also contributed to the recent radiation overdoses of patients treated by linear accelerators. One report from the New York Times [5] quotes Dr. James Thrall, professor of radiology at Harvard Medical School and chairman of the American College of Radiology, saying, “There is nothing on the machine that tells the technologist that they’ve dialed in a badly incorrect radiation exposure.”

Medical device software must accommodate inevitable human errors without affecting patient safety. Moreover, the specification of requirements should take into account all the key stakeholders. For instance, it is believed that some infusion pump manufacturers specify requirements based mostly on interactions with physicians rather than the primary operators of the pump: nurses. When nurses become disoriented and frustrated using infusion pumps, operational problems can result. Inadequate attention to human factors during specification of requirements will promote hazardous situations.

3.5 Mitigate Low-Probability, High-Consequence Risks

Manufacturers, health care professionals, and users often put too much confidence in medical device software. *It can't happen here. There are no reported problems.* Such statements have only a shallow basis in fact, but lead to a false sense of security. The manufacturer of the Therac-25

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Sidebar 2: Threats, Controls, and Vulnerabilities from Pflieger and Pflieger [44].

A threat to a computing system is a set of circumstances that has the potential to cause loss or harm. To see the difference between a threat and a vulnerability, consider the illustration. Here, a wall is holding water back. The water to the left of the wall is a threat to the man on the right of the wall: The water could rise, overflowing onto the man, or it could stay beneath the height of the wall, causing the wall to collapse. So the threat of harm is the potential for the man to get wet, get hurt, or be drowned. For now, the wall is intact, so the threat to the man is unrealized. However, we can see a small crack in the wall—a vulnerability that threatens the man's security. If the water rises to or beyond the level of the crack, it will exploit the vulnerability and harm the man.

linear accelerator, which killed and injured a number of patients with radiation overdoses, initially responded to complaints from treatment facilities that, "the machine could not possibly over treat a patient and that no similar complaints were submitted to them [29, 30, 11]." It is very difficult to reproduce problems in software—often leading to denial rather than discovery of root causes. This difficulty derives in part from the complexity of a device's system-of-systems architecture and from the embedded nature of the system (See Section 2 for further discussion).

Security and privacy fall into the category of low-probability, high-consequence risks that could lead to widespread problems with little or no warning. Problems range from downtime to intentional harm to patients. Because devices can easily connect with physically insecure infrastructure such as the Internet and because software vulnerabilities (Sidebar 2) are often discovered with little or no warning before threats exploit the vulnerability [48], security and privacy outcome measures should play a central role for all major aspects of software development of medical device software (specification, design, human factors, implementation, testing, and maintenance).

"Patients who receive treatment from a potentially lethal medical device should have access to information about its evaluation just as they have access to information about the side effects and risks of medications."— Report on *Software for Dependable Systems: Sufficient Evidence?* by the National Research Council of the National Academies [10, p. 91]

Specification of requirements should address low-probability, high-consequence risks. If a high-consequence risk proves too difficult or costly to mitigate, health care professionals deserve to know about the risks no matter how small.

Innovations in wireless communication and computer networking have led to great improvements in patient care ranging from remote, mobile monitoring of patients (e.g., at-home monitors

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Sidebar 3: Medical devices are susceptible to malware.

Medical devices are no more immune to malware (e.g., viruses, botnets, keystroke loggers) than any other computer. Computer viruses can delete files, change values, expose data, and spread to other devices. A computer virus does not distinguish between a home computer and a hospital computer. Yet in the health care setting, the consequences of malicious software could lead to less effective care (e.g., corrupted electronic medical records that necessitate re-testing) and diminished safety (e.g., overdoses from infusion pumps, radiation therapy, or implantable medical devices). For these reasons, vendors may advise health care providers to install anti-virus software with automated Internet-based updates. However, these products introduce risks that can themselves reduce the trustworthiness of the medical device software. When McAfee released an automated update of its virus definition files, the anti-virus product incorrectly flagged a critical piece of Windows software as malicious—and quarantined the software [32]. This disruption of a critical file caused a number of hospitals to suffer downtime. Medical systems were rendered unavailable.

for cardiac arrhythmias or diabetes) to reduced risks of infection as a result of removing computer equipment from the sterile zone of an operating room (e.g., wireless wands for pacemaker reprogramming). However, the increased interconnectedness of medical devices leads to security and privacy risks for both medical devices in the hospital and in the home [25, 19, 33]. For instance, there is no public record of a specification that requires a home monitoring device *not to be physically capable* of reprogramming an implanted cardiac device. Thus, a malicious piece of software could change the behavior of a home monitor to quietly disable therapies or even induce a fatal heart rhythm—without violating the public specification.

4 Policy Recommendations for Trustworthy Medical Device Software

Regulatory and economic policies should promote innovation while incentivizing trustworthiness in a least burdensome manner. Although one study of medical device recalls concludes that the economic impact of poor quality does not in general have severe financial penalties on the affected company [51], policy recommendations below focus on technical and managerial issues rather than financial penalties or incentives.

4.1 Specify Outcome Measures, Not Technology

The safety and effectiveness of software-based medical devices could be better regulated in terms of outcome measures rather than in terms of specific technologies³. The regulatory infrastructure should aim at making industry meet meaningful goals and show proof of achieving such goals.

The push toward prescriptive standards leads to an oversimplification in that the trustworthiness of a device depends on context. For example, one FDA notice advises to “update your operating system and medical device software [15].” However, software updates themselves can carry risks that should be either accepted or mitigated depending on the situation specific to each

³In Europe, the legal definition of a medical device explicitly mentions software [18]. In the United States, the legal definition of a medical device is less specific.

medical device. On a desktop computer used to update a portable automated external defibrillator (AED), it might be reasonable to routinely update the operating system even if there is a risk that the update may fail in a manner that makes the desktop machine inoperable. However, updating the operating system on the defibrillator itself carries a risk that failure could render the AED inoperable. A hospital that updates all its devices simultaneously is vulnerable to system-wide inability to provide care.

Rather than prescribe specific technologies, regulatory policies should incentivize manufacturers to specify meaningful outcome measures in the context of the given device and be required to prove such claims. Lessons from evidence based medicine [42] could assist in creating outcome measures for trustworthy medical device software.

4.2 Collect Better Statistics on the Role of Software in Medical Devices

Many questions about the trustworthiness of medical device software are difficult to answer because of lack of data and inadequate record keeping. Questions include:

- To what degree are critical device functions being performed by software (vs. hardware)? Is the amount increasing? Decreasing?
- What effect does software have on reliability? Availability? Maintainability? Ease of use?
- How do these software characteristics compare with similar implementations in hardware? Does the software make the device safer or more effective?
- What does data from the predicate device reveal about the new device? Does predicate data save time in specification of the new device? Does predicate data save time in testing of the new device?

Many record keeping tools are already in place (e.g., the MAUDE adverse events database and the recalls database at FDA). However, these tools are severely underutilized. Databases suffer from severe underreporting. For example, in the same time period there are only 372 adverse event reports in MAUDE that cite "computer software issues" despite there being well over 500 entries in the recall database that cite software as a reason for the recall. At the VA, "over 122 medical devices have been compromised by malware over the last 14 months" according to House testimony [1]. But there are no records in MAUDE citing a "computer system security issue"⁴.

Scott Bolte of GE Healthcare emphasizes that for security problems, formal reporting is especially lacking [6]:

"Although there is a lot of anecdotal evidence that malicious software has compromised medical devices, there is a notable lack of formal evidence. So without this formal reporting, the FDA is limited in its ability to act or intervene. Reporting is something providers and arguably the manufacturers themselves can and should start doing immediately."

Policies should encourage better reporting of adverse events and recalls. Otherwise it will only be possible to point out anecdotal failures rather than confidently point out trends for successful products that epitomize innovation of trustworthy medical device software.

⁴On July 12, 2010, it was determined that two bogus MAUDE records classified under a "computer system security issue" were not actually related to computer security.

4.3 Enable Open Research in Software-based Medical Devices

The highly proprietary nature of the medical device software industry makes it difficult for innovators to build upon techniques of properly built systems. Some information may become public after an accident, but this information teaches about failure rather than success. More open access to success stories of engineering medical device software would lead to innovation of safer and more effective devices. The NITRD report [39] explains that:

"Today we have open-research platforms that provide highly effective support for the widespread dissemination of new technologies and even the development of classified applications. The platforms also provide test beds for collaborations involving both researchers and practitioners. One spectacular example is the Berkeley Motes system with the TinyOS operating system."

"The medical-device community could benefit from the existence of such open-research platforms. They would enable academic researchers to become engaged in directly relevant problems while preserving the need for proprietary development by the industry. (TinyOS facilitates academic input even on government-classified technology, which is an example of what is possible.)"

"An open research community needs to be established comprising academics and medical device manufacturers to create strategies for the development of end-to-end, principled, engineering-based design and development tools."

4.4 Clearly Specify Roles and Responsibility

In complex systems of systems that rely on software, it is difficult to pinpoint a single party responsible for ensuring trustworthiness of software because the property is of the system of systems rather than of individual components. A modern linear accelerator is an example of a complex system of systems because commercial off-the-shelf (COTS) software such as Windows may serve as the underlying operating system for a separately engineered software application for planning and calculation of dose distribution. An embedded software system then uses the treatment plan to control mechanical components that deliver radiation therapy to a patient. When different entities separately manage software components in complex systems of systems, system-level properties such as safety are more difficult to ensure because no single entity is responsible for overall safety.

The FDA notes that a key challenge is a shared responsibility for failures in software [15]. If the user updates the software on a medical device, then is the manufacturer truly at fault? If a medical device relies on third party software such as operating systems, then who is responsible for maintaining the software?

Technology alone is unlikely to mitigate risks that stem from system-level interactions of complex software designed by different organizations with different agendas and outcome measures. The problem is likely intractable without a single authority responsible for the trustworthiness of interfaces between interacting systems. The interface between medical device application software COTS software is a common battleground for disclaimers of responsibility (See Sidebar 4).

Leveson [30, Sec. 4.2.1] points out that diffusion of responsibility and authority is an ineffective organizational structure that can have disastrous effects when safety is involved. The British

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Sidebar 4: Take Service Pack 3 and see me in the morning.

Medical devices can outlast the underlying operating system software. Many medical devices rely on commercial off-the-shelf (COTS) software, but COTS software tends to have a shorter lifetime for expected use than a typical medical device. For instance, Microsoft mainstream support for Windows XP lasted for less than 8 years (December 2001–April 2009) [36], whereas an MR scanner may have an operational life of ten to twenty years [6].

It is not uncommon for a newly announced medical device to rely on operating system no longer supported by its manufacturer. Microsoft ended support for security patches for Windows XP Service Pack 2 and advises vendors to upgrade products to Service Pack 3. But hospitals often receive conflicting advice on whether to update software. House testimony [24] mentions that,

"As a sobering side-note, over the last three weeks, in collaboration with a researcher from Georgia Tech in Atlanta who is involved with the Conficker Working group, I have identified at least 300 critical medical devices from a single manufacturer that have been infected with Conficker. These devices are used in large hospitals, and allow doctors to view and manipulate high-intensity scans (MRI, CT Scans etc), and are often found in or near ICU facilities, connected to local area networks that include other critical medical devices.

Worse, after we notified the manufacturer and identified and contacted the hospitals involved, both in the US and abroad, we were told that because of regulatory requirements, 90 days notice was required before these systems could be modified to remove the infections and vulnerabilities."

Users of medical PACS (picture archiving and communication system) struggle to meet conflicting requirements: medical device manufacturers who require health care facilities to use old, insecure operating systems and FDA guidelines that advise keeping operating systems up-to-date with security patches. One anonymous posting on a technical support web site [8] reads:

"I am setting up a medical imaging facility and I am trying to do the same thing as well. The PACS system we are integrating with is only compatible with SP2. I order 6 new Dell workstations and they came preloaded with SP3. There are actual versions of programs out there that require SP2. For instance, the \$250,000 Kodak suite I am installing. Plus a \$30,000/yr service contract. This holds true for the majority of the hospitals which have PACS systems.

However, if what you are saying is true then I found something useful within your post. You stated 'if you installed XP with integrated sp3, it is not possible to downgrade sp3 to sp2,' is this true? Do you have any supporting documentation as this would be very helpful so that I can provide Dell with a reason why I need to order downgraded XP discs."

The plaintive quality of this call for help provides insight into how helpless some users feel because of the diffusion of responsibility for maintaining COTS software contained within medical devices.

Ministry of Defence [41] provides a good example of clear roles and responsibilities for safety management of military systems. The ideas apply broadly to critical systems and may work well for medical systems.

4.5 Clarify the Meaning of Substantial Equivalence for Software

In the context of the 510(k) pre-market notification process, demonstration of "substantial equivalence" to a previously approved "predicate" medical device allows a manufacturer to more quickly seek approval to market a medical device.

Imagine if the predicate device has a function implemented in hardware, and the manufacturer claims that the new version is substantially equivalent because the only difference is that the new version is implemented in software. Because hardware and software exhibit significantly different behavior (see Section 2), it is important that the design, implementation, testing, human factors analysis, and maintenance of the new device mitigate the risks inherent to software. However, this difference casts doubt on substantial equivalence because of the different technological characteristics that raise different risks to safety and effectiveness. Furthermore, when does a software-related flaw in a recalled predicate device imply that the same flaw exists in the new device?

As was noted at the Institute of Medicine Meeting #2 on Public Health Effectiveness of the FDA 510(k) Clearance Process in June 2010, there is doubt on whether hardware can act as a predicate for functions implemented in software:

"One of the interesting classes is radiation equipment...even the software, which I wonder where they got the first predicate for software."

–Dr. David Feigel
Former Director
FDA Center for Devices and Radiological Health (CDRH)

The interpretation of substantial equivalence needs clarification for software-based medical devices.

4.6 Increase FDA Access to Outside Experts in Software Engineering

The FDA should increase its ability to maintain safety and effectiveness of medical devices by developing a steady pipeline of human resources with expertise in software engineering for critical systems.

Various offices within FDA's Center for Devices and Radiological Health employ a small number of software experts. FDA also has a number of successful fellowship programs including the Commissioner's Fellowship Program, the Medical Device Fellowship Program, and the Device Evaluation Intern Program to attract students and experienced experts from medical and scientific communities. However, software experts are notably underrepresented in these programs. The Web page for the Medical Device Fellowship Program⁵ targets health professionals, and other

⁵<http://www.fda.gov/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/MedicalDeviceFellowshipProgramCDRH/default.htm>

Sidebar 5: Substantial Equivalence: Paper or plastic?

An interesting thought experiment is to ask how the trustworthiness of electronic health records differ from traditional paper records. FDA generally does not consider a paper medical record as a medical device. However, FDA may consider an electronic health record as a medical device. Adding automated algorithms to prioritize display of data from an electronic medical record would shift the system toward regulation as a medical device.

Paper records are subject to threats such as fire, flood, misplacement, incorrect entry, and theft. Paper records are cumbersome to backup and require large storage rooms. But electronic records introduce risks qualitatively different from paper records. Making changes to a paper record tends to leave behind physical evidence that is auditable, but making electronic records auditable requires intentional design. A single coding error or errant key press could lead to destruction of an entire collection of electronic records—especially for encrypted data. The speed of technology can make electronic record keeping easier, but can encourage bad habits that lead to difficult to detect mistakes. For instance, a computer display that clears the screen following the completion of an operation makes it difficult to trace back a sequence of changes.

Overconfidence in software for electronic medical records could lead to financially-motivated decisions to discontinue paper-based backup systems. One full-scale failure of a clinical computing system at the Beth Israel Deaconess Medical Center lasted four days—forcing the hospital to revert to manual processing of paper records [25]. While paper-based backup procedures allowed care to continue, few of the medical interns had any experience with writing orders on paper. When health care professionals struggle with technology, patients are at risk.

Heated debates about paper versus electronic recording appears in other contexts such as voting. A National Academies report [7] provides context for the electronic voting debate with arguments applicable to the safety and effectiveness of electronic medical records.

existing programs primarily target biomedical engineers rather than software engineers. Of the fifty Commissioner's Fellows selected in 2009, none had formal training in computer science⁶. In 2008, one of the fifty fellows had a computer science degree, but did not work in the Center for Devices and Radiological Health. A former FDA manager indicated that software experts rarely participate in these fellowship programs. Another person familiar with FDA processes noted that seldom does an FDA inspector assigned to review a 510(k) application have experience in software engineering—even though the majority of medical devices today rely on software.

The FDA should expand its access to outside experts for medical device software by creating fellowship programs that target software engineers. For instance, FDA could more aggressively recruit students and faculty from computer science and engineering—especially individuals with advanced training in software engineering topics such as system and software safety, dependable computing, formal methods, formal verification, and trustworthy computing.

⁶<http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/CommissionersFellowshipProgram/UCM216921.pdf>

5 Summary

The lack of trustworthy medical device software leads to shortfalls in safety and effectiveness, which are inextricably linked with properties such as usability, dependability, reliability, security, privacy, availability, and maintainability. Many risks of medical device software could be mitigated by applying well-known systems engineering techniques, especially during specification of requirements and analysis of human factors. Today, the frequency of news reports on tragic, preventable accidents involving software-based medical devices falls somewhere between that of automobile accidents and airplane accidents. Event reporting on tragic medical device accidents is likely headed toward the frequency of the former given the continued increase in system complexity of medical device software and present-day regulatory policies that do not adequately encourage use of modern software engineering and system engineering practices.

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The Honorable Senator Herbert H. Kohl
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April 13, 2011

The Honorable Senator Bob Corker
Ranking Member of the Senate Special Committee on Aging
United States Senate
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Re Congressional Hearing:
"A Delicate Balance: FDA and the Reform of the Medical Device Approval Process"

Dear Senator Kohl,

Thank you for the opportunity to address a statement for the record. I really appreciate it. In my statement today, I would like to address a letter written to the American Public by Dr. Jeffrey Shuren, current Director of the CDRH, which accompanied an FDA News Release dated January 19, 2011 and also a "Plan of Action for Implementation of 510(k) and Science Recommendation" each of which is attached.

"These actions will result in 'a smarter medical device program that supports innovation, keeps jobs here at home, and brings important, safe, and effective technologies to patients quickly,' said Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health (CDRH)."

Thank you. For the last few days I have debated on the direction this statement to you would take. There are so many things I wish to say to this committee it is so very hard to narrow it down to just one area of what has been a 4 year nightmare for myself and my family. I have decided to start at the beginning.

The FDA's oversight of the safety of medical devices. That is where it all began for me. The role of governments' most basic responsibility is to protect her citizens. If she fails at this she fails at her most important obligation.

I have attached a letter from the Center Director, Dr. Jeffery Shuren to the American Public. It is my opinion that the FDA has clearly failed to meet its most basic obligation for which the agency was created: to protect the public.

Today I ask you only one question: WHAT IS THE ACCEPTABLE NUMBER?

It would have given me greater confidence in the quest to change the direction of the FDA mentioned by Dr. Shuren to assure the safety and effectiveness of medical

technologies used by and on patients if that wish would have been placed before the desire to foster medical device innovation.

When did patient safety become the agency's second mission.

The letter's next 5 paragraphs only speak to the desire of Dr. Shuren to keep the United States the leader in medical device innovation.

In paragraph 6 we now have mention of the safety of these medical devices. In this process of innovation the FDA will now seek to focus on two areas - one to review the program on how to strengthen the program and the other to make the process more predictable. Did I miss the part in this quest which addresses the issue: Is the product safe to use on the American public? The agency did engage the public at town hall meetings for their feedback, one of which I attended and will discuss later in this statement.

The letter goes on to state " While no medical device is completely risk free, the FDA is strengthening its capacity to assess medical devices and monitor their safety once they are on the market and being used. " It is at this point in Dr. Shuren's letter I find myself having a difficult time with my breathing and a sincere desire to keep my head from wanting to spin itself around.

Medical devices should have clinical studies to ensure their safety before it is used on the American public. This statement being said is what the American public have been lead to believe.

If medical devices are being cleared for public use without clinical trials for safety and efficacy, they should all be labeled with a buyer beware...to the consumer, not just to the doctor. They should clearly state on their packaging that no clinical trials were done for the specific intended use of the product. The role of governments most basic responsibility is to protect its citizens from known harm. If it chooses not to do this I have to ask: **WHAT IS THE ACCEPTABLE NUMBER OF AMERICANS HARMED** before the FDA is willing to put the publics' safety before the desire to foster medical device innovation.

This is my story:

My name is Janet Holt. I am an American citizen and I live in the great state of Texas. Until the year 200, we were living proof of the American dream. We worked hard, invested our money, saved what we could, took our own risks, and our handshake was as good as any written contract. We are entrepreneurs. We live in Texas, so ranching has to be one of the things we must do well. We run approximately 300 mother cows on about 800 acres raising purebred Angus and Polled Hereford Cattle. We own 5 Franchise restaurants in 4 cities and employ around 300 people. We rise before the sun does and quit long after the sun goes down. In the cattle business, we strive to produce the best beef cattle, building on 25 years of hard work and knowledge. In our restaurants we serve great food, provide safe working conditions, provide and pay our employees

everything we can. We are good people.

In 2007 I had just finished building our 5th restaurant. It was quite a task. It was our most expensive venture to date. I laid awake at night worrying if we had made the right decision with our capital. You see, we have 300 employees that depend on us every day to make the right decision. They buy their cars, their homes, and build their own dreams all the while depending on us for their future.

Just after we had opened this last restaurant I felt something was wrong with me medically. I made an appointment with my Ob/Gyn who had been my doctor for over 20 years. After a quick examination he said my bladder had prolapsed as well as my uterus. He said not to worry. After surgery he would have me back to work in 2 weeks. I discussed this with my husband and we decided he could cover me for the 2 weeks. It would be a long two weeks with only one of us trying to cover everything we do.

Well it has been more than 3 years and I have yet to return to work full time. You see I had a procedure using a mesh kit made by AMS that placed propylene mesh permanently inside my body. I now know this product was cleared, *not approved*, thru the 510K process. I have had horrific complications from the mesh requiring 7 repair/removal surgeries. The mesh shrank. It folded. It eroded thru the vaginal walls. It abscessed out the creases of my leg/groin areas. It has finally been removed, although I still need to see a wound doctor weekly because my leg/groin area had been cut open 3 times in the same place. The wound/incision has been open since last July and is having a very difficult time closing.

My insurance company has paid out almost \$500,000.00 (½ million) dollars and the total is still growing. I have paid my yearly deductibles, my co-pays, my 10%, my travel expenses once for surgery in Dallas and 3 surgeries in LA, spending weeks in hotels before I could travel home. All of these substantial losses of my health, quality of life and finances are because of a medical device, probably selling in the low thousands with a profit less than that. It has ruined my life.

Dr. Shuren noted in his letter to the American public “that medical devices in the U.S. have a strong track record of safety and effectiveness. The 510k program which the FDA created approximately 30 years ago, has helped support a robust medical device industry in the U.S. and helped stimulate innovation by providing a pathway for medical devices to come to market without the complexity of the approach used for high-risk devices.”

Once again my head wants to spin completely around. What is low-risk about permanently placing mesh inside a women’s vagina? What they are really saying is we placed his product on the market without understanding the risk and long term effects without requiring any post market clinical trials. WHAT? When is any medical device that is permanently placed inside a human body low-risk?

The complication rate of mesh in prolapsed repair is reported to be from 0 to 23%. However, mesh complications are difficult to quantify because there is no true

denominator for the number of vaginal surgeries that use mesh. No registry exist for the placement of mesh in the vagina for the treatment of pelvic floor dysfunctions.

The FDA has the MAUDE database. However, because of its voluntary nature it does not reflect the real number of complications. Even fewer complications are reported in the published literature. For example, in a 4 year period a Medline search confirmed 86 major complications of sling mesh in 11,800 cases. In the same time period, the MAUDE data base reported over 900 complications with 161 major complications and 10 deaths.

At the town hall meeting I attended, Dr. Shuren stated that a new reporting data base was being put in place. However if there is still no true denominator for the number of vaginal surgeries that use mesh how are they to be reported? Once again I feel the need to reach for the duct tape I purchased years ago at the suggestion of Homeland Security so I can tape my head so it will not spin around. **What is the acceptable number of women injured** before the FDA is willing to do more? At the CDRH Town Hall meeting, I suggested a need for a mandatory reporting system with a registry for mesh used in the treatment of pelvic floor dysfunctions. I reported that many countries already do.

Dr. Shuren suggested that it was not the place of the United States to follow other countries. The U.S. should lead. Well that is a wonderful thought if we were actually in the lead on this important reporting system. When in business we get to the place where we think we can no longer learn from others, that we have all the answers, we have entered into a dangerous area of thought that can put us in a position of weakness. Even a country as great as ours does not have all the answers to the questions before us with all the new technology available.

This request for a mandatory reporting system has been asked for many, many times by some of the most respected surgeons who are on the front line. Those surgeons who are asked to fix the problems caused by no clinical trials on those so called low-risked medical devices. It was stated we do have mandatory reporting by hospitals (user facilities) for a required second surgery. That may work for some reporting but when you have a medical device that was cleared thru the 510k process permanently placed inside your body, you may have multiple surgeries done in different hospitals by different surgeons. How are these to be reported?

As we enter a time in history with the greatest number of baby boomers entering the system we have to ask who is going to pay for the health care of these citizens when no clinical trials are needed for those medical devices cleared thru the 510K process.

Is it the role of government to assist and pay for those clinical trials on unknowing senior citizens? Is it the role of government to pay for the additional medical care needed for sometimes permanently injured citizens for damage done by a these medical devices? What part of the responsibility lies with the medical device manufacturers who have made billions of dollars on a marketed product because no clinical trials were paid for by their companies?

WHAT WILL BE THE ACCEPTABLE NUMBER OF PATIENTS (BOOMERS)
INJURED BEFORE THE FDA WILL REQUIRE MORE FROM THE MEDICAL
DEVICE MANUFACTURERS?

My story looking forward:

I now lay awake at night wondering what will happen to those 300 people whom we employ. My family has gone thru all of its savings. We built a business that took both of us working every day. We never took a day off. We never went on a vacation together. We worked for 30 years building a successful business. It took both of us. What went from a 2 week needed recovery to an almost 4 year leave. The hours needed to run our business are just too many for one person. My husband went from working 70 hours a week to working 80. He just couldn't be everywhere. The lack of supervision was a direct cause of 100s of thousands of dollars in losses, this from a company that had been profitable for the past 30 years. We were just about to retire. My husband has cashed in his 401k. We have borrowed against all of our insurance policies. We loaded cattle by the trailer loads and shipped them to market. It has been a very long hard road my family has traveled thru no fault of its own. We built our business based on two working owners. Four (4) years is a very long absence of one of the owners. I wish I could say we have endured the crisis well. The losses to our businesses have been heavy. We have cashed in all we could to ensure the employment of those who work for us. For those who trusted us to always make the right decisions.

Well we made a wrong one when we thought all medical devices put on the market for patient use were safe, that they were tested thru clinical trials. We were deadly wrong. **Our family has paid a very high price for the trust we placed in the FDA.** As we struggle still to try to survive this crisis, sleep does not come easy.

We will survive. We are Texans. We gave our word to our employees and to the banks that loaned us money to grow. At our age we will never be able to recover those losses. After the 7 surgeries I am as good as I am going to get. I am planning on returning to work as soon as I am released from all the doctors I see now. It should be soon, hopefully. I am looking forward to doing what I can.

I can say one thing for sure I will never trust the FDA to ensure my safety in medical issues. My mother called a few months ago after a doctor visit to ask me what kind of mesh did I have put in. I asked her why she wanted to know. She informed me her bladder had prolapsed. He doctor said he would like to schedule a procedure using mesh to fix her problem. She started to inform the doctor of her daughter's nightmare with mesh. He told her not to worry. *That was the old mesh. They had new mesh now.* This was better. There were no problems with it now.

I felt the color drain from my face. I asked, did the doctor show or inform you of the FDA warning that had been placed on mesh? She said no. What good does it do for the FDA to place a warning on a product if it has no enforcement to see that patients are told. I told my mother she should have ran out of his office screaming at the top of her lungs.

WHAT IS THE ACCEPTABLE NUMBER OF INJURIES NEEDED BEFORE THE
FDA WILL ACT?

The role of government most basic responsibility it to protect her citizens. Especially as we grow old. If she fails at this she fails at her most important obligation. I am not against new technology. I just don't want to take part in clinical trials I am not aware I am in. For those who have spoke before me and will speak after me in advocating the use of mesh I have to say shame on all of you. If what has happened to me would have happened to your wife or mother I would find your ability to speak on behalf of mesh in a women's pelvic floor impossible.

Could it be that our judgment is so clouded by industry and the input from them that we are blinded to see the obvious? It is time to admit the use of synthetic surgical mesh material, especially between the bladder and the vagina, has been a surgical experiment that failed. If clinical trials had been done on mesh and other medical devices placed permanently inside your body, I wonder how many medical devices on the market today would have ever been approved. Dr. Shuren closed his letter saying "here at the FDA, we want safe and effective devices brought quickly to market, too- not only are we doctors, nurses and other healthcare professionals but we, our friends and our families, are also patients."

I personally would like to see them brought to the market as safe and effective devices that have been thru clinical trials. The American people are not guinea pigs available for the medical device manufacturers. We are human beings with hopes and dreams who at one time believed in the FDA.

What is the acceptable number of women injured or who have died needed before our government will protect us?

I plead with this committee to demand patient safety be the number one priority of the FDA.

I am extremely grateful for the opportunity to have participated in this process.

Janet Holt



April 11, 2011

The Honorable Senator Herbert H. Kohl
Chairman of the Senate Special Committee on Aging
United States Senate
330 Hart Senate Office Building
Washington, D. C. 20510

The Honorable Senator Bob Corker
Ranking Member of the Senate Special Committee on Aging
United States Senate
Dirksen Senate Office Building SD-185
Washington, D.C. 20510

Re Congressional Hearing:
"A Delicate Balance: FDA and the Reform of the Medical Device Approval Process"

Dear Senator Kohl,

I want to thank you and Ranking Member Senator Bob Corker for the opportunity to address a statement for the record today. As a baby boomer, I really appreciate your continuing leadership in supporting and caring for seniors.

The Food and Drug Administration's Strategic Action Plan "Protecting and Advancing America's Health: Responding to new challenges and opportunities" published in August 2003 focused on obesity, putting forward ways to stop it by making consumers more aware of what they were eating. It was an important step and a lot of the premises put forth (as excerpted below) were really good.

FDA Mission Statement

The FDA, recognized as the gold standard for food and drug safety and effectiveness, is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more

effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

Page 18 – Empowering Consumers: Improving Health through Better Communication:

Enable consumers to make smarter decisions by getting them better information to weigh the benefits and risks of FDA-regulated products.

“For all that FDA’s efforts to improve enforcement and regulatory protections for the public, as well as to help encourage the development of safer, more effective, and affordable food and medical technologies, people through their own choices can have an even greater impact on improving their health.”

Page 24 – Improving Patient and Consumer Safety: Seek continuous improvements in patient and consumer safety by reducing risks associated with FDA-regulated products.

“More mortality, morbidity, and related costs could be avoided as FDA improves the management of product related risks.”

If the FDA’s Strategic Action Plan of 2003 was put into practice today in relation to medical devices cleared through the 510 (k) pathway, a lot of consumers would be making different decisions. Many would probably not have surgery if it involved synthetic surgical mesh. But surgical mesh has followed the trends of other flawed devices.

A lot of people got injured, the FDA became aware and put out info to doctors to deal with the complications after the fact. To me it seems a revolving door for injuring patients, clearing products through the 510(k) and then figuring out how to deal with the complications, rather than preventing the complications in the first place.

It just seems like a continuing pattern. The FDA always seems to be in a reactive position as opposed to a pro-active position, always trying to curb the actions of industry after the fact but never ahead of the curve.

There is a Special Guidance Document for Surgical Sutures created in June 2003. Although sutures are the predicate device for surgical mesh, there is no special guidance document for mesh, a much more complicated medical device.

There is a report on Laparoscopic Trocar Injuries issued by the FDA in November 2003. <http://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm197339.htm> It taught doctors how to minimize injury from trocar use.

Both of these seem very similar to the problems with mesh. That's why I recommend a proactive approach on the part of the FDA, as opposed to waiting for the next disaster: more hip implant recalls, elbow replacement recalls, or bad leads in a defibrillator.

I know there is a "Plan of Action for Implementation of 510(k) and Science Recommendations" currently being put in place. But will this end the cycle of figuring out how to deal with major complications after the fact? What will happen to all of the harmful medical devices currently being sold? Will those patients ever know the truth about what ruined their lives?

The FDA needs a better business plan. Running the FDA is not a medical diagnosis where you try different therapies to see which one heals the patient. You find a successful process and stick with it. The FDA's internal operations is a work environment requiring definitive standard operating procedures with clear guidelines for the decision making process of all employees. The 510(k) does not provide those guidelines.

It seems there is too much decision making left to the individual employee at FDA. There has to be a uniform decision making process: when to use certain available regulatory authorities, what to do when there is no honest denominator needed to make a decision, etc in relation to the 510(k). The clearance process itself is pretty straightforward but how the FDA should deal with defective medical devices post market is not clear. It only takes 30 to 90 days to clear a device, while post market decisions to stop harm from complications may take years.

Employees need better training in all of the FDA's regulatory authorities whether the employee works in Premarket Approval, Post Market Studies or Compliance. Every employee needs to understand the whole process.

If a team leader is put in place for a particular medical device, they need to remain the team leader. Too much investment of time and knowledge is lost when one team leader is replaced with another.

Class I & Class II medical devices cleared through the 510(k) Premarket Notification pathway do not require proof of safety or efficacy from clinical trials. The FDA does, however, require "*proof of harm*" over a period of years to take action against the same medical devices cleared in less than 90 days but never proven to be safe or effective in the first place. This makes no sense and causes a lot of harm while the FDA decides how to take action, if it ever does.

The FDA needs to be a wholly independent agency, with more definitive regulatory authority, well funded, well staffed and not dependent on industry fees. The FDA is a regulatory authority and should not have to depend on the very companies it regulates for money.

As in my statement at a workshop of the Institute of Medicine Committee reviewing the Public Health Effectiveness of the 510(k) Clearance Process (June 14, 2010), I recommend the following changes to the 510(k) clearance process (copy attached):

- 1) Educate the American public about the difference between Pre Market Approval and Pre Market Notification Clearance Process.
- 2) Make patient labeling mandatory for all medical devices.
- 3) Make reporting mandatory with clear consequences for silence by doctors, hospitals and medical device makers.
- 4) Create a very specific guide for the FDA/CDRH to make better use of their regulatory authority. The decision making process for when and how to use FDA's regulatory authority should not be left to the discretion of FDA/CDRH employees.
- 5) Include a mechanism which stops medical device makers from paying doctors to misuse their legal authority to sell products off label to increase the sales of their products.

My recommendations are based on my experience and that of other patient advocates, James P. Shull, Vice President of Truth in Medicine, in particular, with the FDA/CDRH as a patient advocate:

1. You inform the FDA of a serious universal problem with surgical mesh.
2. They request you file an adverse event report on the MAUDE database, despite the fact the database is very inefficient.
3. They request you to ask other patients to file adverse event reports on the MAUDE database.
4. They have conference calls and meetings and communicate with you via e-mails and phone conversations.
5. They issue Public Health Notifications warning of the serious risks and complications of the trans-vaginal placement of surgical mesh. No action is taken to protect or inform the public of the serious risks and consequences of synthetic surgical mesh for hernia repair, a very common procedure most people believe is a safe and simple.
6. They ask you for more information.
7. Eventually a lack of trust develops in this unending process. One becomes extremely skeptical of the FDA, the CDRH, doctors, hospitals and the entire system. You know literally thousands of people are unnecessarily and unknowingly put at risk every day. No action is taken and the cycle continues.

Attached are copies of letters from Michael Leavitt, former Secretary HHS; Dr. Frank Torti, former Principal Deputy Commissioner & Chief Scientist, FDA; Dr. Daniel Schultz, former Center Director CDRH; Senator John Thune of South Dakota and Stephen R. Mason, former Acting Assistant Director for Legislation, HHS dating back to December 2007. All of the letters acknowledge the internal "Action Team" at the FDA looking at the problem of synthetic surgical mesh.

This makes me think about my brother Kem's brother-in-law, Bruce Carlson, who at 56 died of a massive heart attack at a stop light last week. I wonder if it had anything to do with the stent in his heart.

I think of Joleen Chambers' brother who can no longer care for himself because of a failed elbow implant. The CDRH blames it on bad medical care, not the failed device.

I think about my Aunt Jody's friend, Carol McKaig, who had one of the 30,000 failed Teflon TMJ implants (100% failure rate) placed back in 1985. She has never recovered and 25 years later is still having surgeries to repair complications of the failed device.

I think of my steel customer, Hollis Woody, who has had a severe chronic headache for over 30 years now since a failed sinus surgery. He recently discovered, it may not be the sinus surgery at all but instead the amalgam (mercury) fillings placed in his mouth about the same time.

I think of myself. I had a "Copper 7" IUD for birth control for 3 years in my late 20's. Repeated miscarriages prevented me from carrying the second child I always wanted. I later discovered it was probably a side effect of the IUD. Was that a 510(k) cleared device?

And I think of Jim Shull, a man who himself has suffered greatly from surgical mesh, a great partner and friend in this fight to stop the harm from surgical mesh. His pioneering efforts at the FDA opened the door for the changes to come.

Thankfully there are days like today where you have a glimmer of hope the harm caused by unproven, unsafe medical devices will one day stop. Men and women with the power to make real change happen are reading this statement. Your willingness to influence the changes to the Medical Device "Approval" Process to make patient safety number one is very much appreciated. Thank you so much for your time and attention!

Respectfully,
Truth in Medicine Incorporated

Lana C. Keeton

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TRUTH IN MEDICINE INCORPORATED
Mission Statement

Truth in Medicine Incorporated is a patient advocacy organization which educates the public about the potential risks and complications from the implantation of synthetic surgical mesh into the human body. The organization also educates and supports patients who have already been harmed by surgical implantation of synthetic mesh.

Initiatives to Accomplish Our Mission

I. Ask Congress to pass legislation to change All Surgical Consent Forms in regard to Medical Devices/Foreign Bodies when surgical implantation is necessary.

The following information would be on a separate consent form provided to patients 3 days prior to surgery:

- a. Name of any/all medical devices/foreign bodies that are being implanted
- b. FDA approval process of the medical device/foreign body [the 510(k) Premarket Notification approval process, where human clinical trials are rarely required for Class I/Class II devices, or Premarket Approval, where clinical trials are required]
- c. If clinical trials were conducted, what the results of the clinical trials were
- d. All known risks and complications

II. An adverse event report would be provided to each and every patient who has a medical device/foreign body surgically implanted with their hospital/facility discharge papers:

- a. All information related to the medical device surgically implanted in the patient's body will be on the adverse event report when given to patient.
- b. Patients would be alerted to be vigilant for any potential problems. Future medical treatment would be safer because of knowledge of implanted foreign bodies.
- c. Complications could be immediately reported to the FDA by patients. Patients will control the flow of information, as opposed to the health system.

III. Ask Congress to create a Superfund to provide for the medical treatment and/or financial support of patients suffering complications of synthetic surgical mesh medical devices. It will be funded by a tax on all pharmaceutical companies/medical device manufacturers who manufacture and sell synthetic surgical mesh.

BEVERLY J. PENNINGTON

April 13, 2011

The Honorable Senator Herbert H. Kohl
Chairman of the Senate Special Committee on Aging
United States Senate
330 Hart Senate Office Building
Washington, D. C. 20510

The Honorable Senator Bob Corker
Ranking Member of the Senate Special Committee on Aging
United States Senate
Dirksen Senate Office Building SD-185
Washington, D. C. 20510

Re Congressional Hearing:
"A Delicate Balance: FDA and the Reform of the Medical Device Approval Process"

Dear Senator Kohl,

Thank you for the opportunity to address a statement for the record today and for making public a dilemma all Americans face whether they know it or not, an FDA in crisis.

I am Beverly J. Pennington, a baby boomer, a nurse, a patient activist, a Professional Wedding Consultant, a member of Truth in Medicine, and a victim of medical mesh. I became involved with Truth in Medicine in 2009 when I was unable to find medical help for the complications of surgery with surgical mesh. The doctor who implanted a Bard Avaulta Plus vaginal sling was unable to resolve draining wounds 9 weeks after surgery. The organization and its members supported me to find medical care where no one else had answers.

Before surgery, I was advised by my physician that the Avaulta was the best sling on the market. I learned the purpose of pelvic mesh products is to provide vaginal support for prolapsed pelvic organs (POP) and urinary incontinence (SUI) usually caused by weakened muscles due to childbirth, age, and heavy lifting. Unfortunately, after surgery my physician had no answers to my complications. How did that happen? How is it possible the best on the market caused such problems?

I had done some research to make sure having a medical device implanted instead of just sutures was safe and I thought I was in the clear. I didn't find any warnings from the FDA, so I felt it was safe enough for me. I thought it would be the answer to my vaginal prolapse. I felt that if the doctor was recommending it (whom I trusted), and the FDA approved it (whom I trusted), then it was ok. The truth was unavailable through the sources I found. I was uninformed and I was wrong.

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I later found trans-vaginal mesh kits and bladder slings never went through full clinical trials. Apparently they came on the market for use on the unsuspecting public by the 510(k) Premarket clearance process. If only I had known before surgery that in 2008 FDA had issued a letter warning doctors and medical facilities of over 1000 adverse events and complaints from women, ranging from erosion through variant epithelium to bowel, bladder, and blood vessel perforation during insertion of trans-vaginal surgical mesh; discomfort and pain (dysparenia), infection, urinary problems, abscess, and recurrence of prolapse and/or incontinence. Much too late, I also learned treatment of the various complications of mesh can put patients at an increased risk for blood clots, hemorrhage, blood transfusions, reconstruction, pneumonia, disfigurement, paralysis, chronic pain, drainage of abscesses, hematomas, and in some cases even death. How frightening to learn personally of these complications after the fact. Widespread dissemination of basic information from the FDA would have prevented the harm caused to me and thousands of other unsuspecting women.

Here again, the importance of clinical trials cannot be stressed enough! How many women and men will continue to be injured and maimed by mesh before the FDA pulls it from the market?

As a Wedding Consultant, I must have every detail perfect for the bride in order for the event to go perfectly. Of course there are many days and hours spent prior to the special day gathering data, bringing in vendors, budgets, contracts, and planning. Just one small overlooked detail can mean disaster for a consultant and the bride. One minor mistake can cost me my reputation and put me out of business. So, it would only make sense that I would have serious doubts about the 510(k) clearance of Medical Devices with no clinical trials. Serious consequences happen every day to patients because FDA has not taken appropriate measures to keep dangerous products off the market. Playing with the lives of the American public is serious, and it is not taken lightly that so many lives have been catastrophically affected by the use of synthetic surgical mesh.

Medical Facilities (user facilities) are required to report adverse events, but to this date I still have not found mine listed in the Maude Database. As physicians aren't required to report an adverse event for a medical device; therefore making the database is even more flawed with too many inconsistencies and incorrect information.

I believe it should be mandatory for all medical facilities and medical professionals to report to the Maude Database any adverse event involving medical mesh or suffer serious penalties.

So how in the world were medical devices put on the market with the assumption they would be ok for placement in a human without a clinical trial? Of course, the answer is, unknowing guinea pigs...me! The only problem with this is that I never gave my permission to be one of the guinea pigs. To me, the only folks that have benefited from

BEVERLY J. PENNINGTON

medical mesh are the medical device manufacturers who made millions of dollars quickly before the truth came out about how dangerous medical mesh was.

So, it seems to me it was just a guess and a gamble with the lives of the unknowing public to see whether a plastic product made of polypropylene and porcine would work, or in the end be pulled from the market for re-design only to go back on the market as a second or third generation of the same product.

As a victim of the Bard Avaulta Plus mesh, it is really too late for me to ever be completely well or get rid of the mesh 100%. Even the smallest piece of mesh in me now becomes like a giant festering splinter trying to inch its way out causing inflammation in my whole body as it tries to rid itself of the mesh.

I am now facing a fifth surgery (the last one was in November 2010) as more mesh has tracked its way through the vaginal wall. I have suffered greatly from painful bilateral perirectal abscess and emergency surgery to drain them taking nine weeks to close wounds on my buttocks, only to learn there was more tissue tracking granulomas along the remaining mesh arms. So what can be done to correct the defective medical devices? I believe that making it mandatory for all medical devices go through extensive full clinical trials before even thinking of going on the market is crucial in stopping the harm caused by implantation of such dangerous devices.

As a member of Truth in Medicine and a patient activist, I am on a personal mission to get the word out about the dangers in using vaginal mesh and to save others from going through the unnecessary pain and suffering I have. Thank you.

Sincerely,

Beverly J. Pennington
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Thank you Chairman Kohl, Ranking Member Corker and other distinguished members of the Senate Special Committee on Aging for this invitation to submit testimony on some of our findings on our work on medical devices at this important hearing. I am Rita Redberg, MD, MSc, Professor of Medicine and full-time Faculty Member in the Division of Cardiology at the University of California, San Francisco Medical Center. I am Director of our Women's Cardiovascular Service. I am also the chief editor of the *Archives of Internal Medicine*, one of the most preeminent peer-reviewed journals of scientific research in internal medicine. Much of my own research has concerned the appropriate and optimal use of medical devices in patient care, and the journal frequently publishes articles related to use of medical devices.

I am a member of the Institute of Medicine Learning Healthcare Committee. In addition, I am a member of the American College of Cardiology Science and Quality committee, and have served on numerous scientific writing groups for the American College of Cardiology and American Heart Association concerning medical technology and appropriate use of medical technology. I recently chaired the American College of Cardiology and the American Heart Association's writing group on the primary prevention of cardiovascular disease performance measures. I am a member of the FDA Cardiovascular Device expert panel and the California Technology Assessment Forum, which evaluates new medical technologies.

My clinical specialty is in heart disease in women, and I see many women who want to be sure they are getting the best medical care individualized for them. I appreciate the wide choice of medical technology at my disposal in the care of my patients every day. However, it is frustrating that I am often unable to advise my women patients on risks and benefits for them of potentially life-saving devices because of lack of data of safety and effectiveness in women.

Just as I was finishing my cardiology fellowship in 1987, there was a growing awareness that there was a lack of research on women's health, including women's cardiovascular health. It became clear that there were differences in the physiology of heart disease for women and that risks and benefits of many procedures differed by sex. Many new government initiatives at the NIH were set up at that time to address this knowledge gap. In 1988, the FDA specifically called for studies of whether safety and effectiveness were similar within population subgroups defined by characteristics, such as age, sex and race. In 1994, the Office of Women's Health was established within the FDA, and the Center for Devices and Radiological Health instituted a policy to address the possibility of gender bias in submissions and review documentation for new medical devices. This directive stated that all pending and future premarket approval submissions would need to address two important issues, to ensure safety and effectiveness for women as well as men: 1) did the ratio of men and women in the study reflect the underlying distribution of the disease and 2) was there any difference in the safety and effectiveness of the device based on gender?

My UCSF colleagues, Dr. Sanket Dhruva, Dr. Lisa Bero and I recently performed a systematic review of all of the highest-risk cardiovascular devices that received

premarket approval by the FDA between 2000 and 2007 and published this data in a peer reviewed medical journal last month.¹ We examined the FDA's summaries of evidence, which form the basis of the FDA's decision to approve the device. We found that less than three-fourths of these summaries even reported the sex distribution of the patients studied in the clinical trial. When the sex distribution was reported, just one-third of the average population was female. Only twelve percent of studies had more women than men. Even more concerning is that we did not find an increase in enrollment of women over time.

Further, the requirement that the FDA address gender bias for all approved devices was clearly not being met. Only forty-one percent of the summaries contained any statement addressing gender bias. Over one-fourth of the statements identified found a difference in safety or effectiveness of the high-risk device by sex. This is incredibly important because it suggests important differences for these high-risk devices, and it is very possible that the other sixty percent of devices which did not address gender bias still had some differential effect by safety and effectiveness.

Unfortunately, even when gender bias was addressed, all too often the reason for the exclusion of women was inaccurate. This occurred in one summary for an implantable cardioverter-defibrillator, which is a device used to shock patients out of potential lethal heart rhythms. This summary stated, "There were 15 females out of 126 patients (or 11.9%). The relatively low percentage of females enrolled into the study is related to the incidence of heart disease. If females were just as likely to have heart disease as males, then you would expect the percentage to be much closer to 50%."¹¹ This statement inaccurately implies that a very low percentage of women with heart disease, and used this to justify the incredibly poor enrollment of women. Further, based on data predominantly in men, these devices have been used overwhelmingly in women and only recently has data shown that these devices may not have any overall benefit in prolonging the lives of women, although they definitely have many risks given that they are permanently implanted.¹¹

Sometimes when gender bias was addressed, it was done in a way that will only serve to perpetuate the status quo. One representative example is for cardiac resynchronization therapy, which involves a device for patients with heart failure. A clinical trial for this device enrolled just twenty-two percent women. The justification given in the FDA's summary for this poor percentage of women was as follows, "The demographics of the study population are typical for a CRT-D study performed in the US."¹² First, the overall burden of heart failure is actually greater in women than in men. The fact that there has been poor enrollment of women in prior studies cannot be used as justification for future enrollment. If these types of arguments are used to justify the status quo – and we found that they were used in eight separate instances – then they will undoubtedly stymie any progress in the inclusion of women in clinical trials for medical devices.

It is also concerning that some devices are sold and marketed to women without proven safety and efficacy in women. For example, the Thoratec Heartmate II (Thoratec Corporation, Pleasanton, California) is a ventricular assist device which is now FDA

approved for patients with severe heart failure. The device was being advocated for use in women because of its smaller size, but the fact (known prior to device approval) that women were having a three-fold increase in strokes and greater bleeding and infection rates was ignored.^v

The lack of sex-specific data before device approval may lead to delays in discovery of safety and efficacy concerns. For example, registry data of implantable cardioverter-defibrillators (ICDs) shows that women are more likely than men to experience any in-hospital adverse event and major adverse events.^{vi} Safety concerns must be balanced by clinical benefits. However, pooled data indicates that there is no mortality benefit for ICDs for primary prevention in women with heart failure.^{vii} We found that just 28% of participants in studies of electrophysiology devices were women. This incomplete safety and efficacy data may mean that more women are experiencing adverse events for a device lacking a mortality benefit, a situation unlikely to be ameliorated without FDA guidance.^{viii}

The Institute of Medicine also recently issued a report stating that their opinion that “all medical product evaluations by the Food and Drug Administration present efficacy and safety data separately for men and women.”^{ix} It is incredibly important that the FDA require evidence of safety and effectiveness in sufficient numbers of women and sex-specific before they approve these permanently implanted devices. Only with this requirement – and enforcement – will we be able to be more certain that the risks outweigh benefits in both men and women.

^v Dhruva SS, Bero LA, Redberg RF. Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices. *Circ Cardiovasc Qual Outcomes*. 2011;4: 165-171.

^{vi} Summary of Safety and Effectiveness, PMA 000009, Phylax AV ICD, Model 122 382, Software Cartridge SWM1 J-GAV.2.U, Model 128 814, September 2000. (Accessed April 12, 2011 at http://www.accessdata.fda.gov/cdrh_docs/pdf/P000009b.pdf).

^{vii} Redberg RF. Is What is Good for the Gander Really Good for the Goose? *Arch Intern Med*. 2009;169:1460-61.

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^{ix} Dhruva SS, Redberg RF. The need for sex-specific data prior to food and drug administration approval. *J Am Coll Cardiol*. 2010;55:261

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