IMPACT OF MEDICAL DEVICE REGULATION ON JOBS AND PATIENTS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

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IMPACT OF MEDICAL DEVICE REGULATION ON JOBS AND PATIENTS

THURSDAY, FEBRUARY 17, 2011

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

The subcommittee met, pursuant to call, at 9:30 a.m., in room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts, (chairman of the subcommittee) presiding.

Present: Representatives Pitts, Burgess, Whitfield, Shimkus, Murphy, Blackburn, Gingrey, Latta, Lance, Cassidy, Guthrie, Barton, Upton (ex officio), Pallone, Dingell, Towns, Capps, and Waxman (ex officio).

Staff Present: Debbee Keller, Press Secretary; Clay Alspach, Counsel; Cary McWilliams, Legislative Clerk; Jeff Mortier, Professional Staff; Peter Kielty, Senior Legislative Clerk; Chris Sarley, Policy Coordinator; Ryan Long, Chief Counsel, Health; Alan Slobodin, Counsel; Andy Duberstien, Special Assistant to Chairman Upton; Rachel Sher, Minority Counsel; Allison Corr, Minority Policy Analyst; Karen Lightfoot, Minority Communications Director and Senior Policy Advisor; Stephen Cha, Minority Professional Staff Member; and Eric Flamm, Minority Detailee.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order.

The chair will recognize himself for an opening statement.

The United States is the world leader in medical device innovation. According to a recent report, 32 of the 46 medical technology companies with annual sales exceeding $1 billion are based in the United States; and yet the United States is in danger of losing its preeminent status in this field.

Multiple studies have shown that regulatory uncertainty is damaging this critical industry and hurting American patients. For example, the November, 2010, study "FDA Impact on U.S. Medical Technology Innovation" surveyed over 200 medical technology companies; and they described the FDA process as "unpredictable and characterized by disruptions and delays." They also noted that companies are able to make their products available to patients faster and at a significantly lower cost in markets such as Europe.

It already is tough for medical device companies. Only one out of four med tech startups succeed. Half of all reported exits are less

than $100 million, and the total pool of available investment capital is shrinking.

Quite simply, shorter, more predictable, and more transparent approval processes in Europe have led many device companies to seek a market for their products in Europe before submitting them to the FDA; and they are taking good-paying American jobs overseas with them.

In 2008, according to the Lewin Group, the medical device industry employed 422,778 workers nationwide, paid $24.6 billion in earnings, and shipped $135.9 billion worth of products. In 2008, in my home State of Pennsylvania, the medical device industry employed 22,223 people and paid Pennsylvania workers over $1.1 billion in earnings. These are good jobs. Nationally, jobs in medical technology pay almost 40 percent higher compared to the national earnings average.

But this trend does not just hurt our economy. It hurts American patients. American patients on average have access to innovative medical devices 2 years later than patients in European countries and, in some cases, never have access to these devices.

None of us would be concerned about longer, more arduous approval processes for medical devices in the U.S. versus Europe if we thought that those processes kept American patients safer than their European counterparts. But according to recent studies, medical devices marketed through the shorter and more transparent EU processes are statistically as safe as FDA-cleared or approved devices and have comparable patient outcomes.

According to a January, 2011, Boston Consulting Group report, EU Medical Device Approval Safety Assessment, a Comparative Analysis of Medical Device Recalls 2005 2009, "The results of this study suggest little difference between absolute number of serious recalls between the U.S. and EU regulatory systems. The distribution of the serious recalls are similar across therapeutic areas, and reasons for recalls suggesting that differences between the two systems do not ultimately affect performance. In addition, given the expectation that the EU approves more devices than the U.S., it is likely that the EU recall rate may actually be slightly lower than the U.S. rate."

We need to ensure that our regulatory system is consistent and transparent so American patients have timely access to life-saving and life-improving drugs and devices and American workers have access to these goods.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

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We need to ensure that our regulatory system is consistent and transparent so American patients have timely access to life-saving and life-improving drugs and devices and American workers have access to these good jobs.

I yield the remainder of my time to the chairman emeritus, Mr. Barton.

Mr. PITTS. I yield the remainder of my time to Chairman Emeritus Mr. Barton.

Mr. BARTON. Thank you, Mr. Chairman. You surprised me, but I do appreciate it. Thank you for holding this hearing.

Back in 1997, as the chairman of the Oversight and Investigation Subcommittee, I had the great privilege to work with Congresswoman Eshoo on the Medical Device Regulatory Modernization Act of 1997. That became part of the Food and Drug Modernization Act called FDAMA. We worked to ensure that the FDA operates in the best interest of patients by ensuring that they have access to new life-enhancing and life-saving technologies. We and others realized that the regulatory process for medical devices needed to be reformed in order to get medical devices to patients in a timelier fashion, to spur medical innovation, and to help draft small business job creation.

Today, it appears to me these reforms have been successful. It doesn't mean that we can't improve on it. We do not want to backtrack on this success, and we do not want to make it harder on the small businesses and manufacturers to get new and vital medical devices into production and into the market.

Texas is the leader in medical device innovation. There are over 4,000 medical equipment and device companies in my State. Most

of them are relatively small. Texas and America depend on job creation in this sector with a market that is open and has reasonable regulations.

Lack of transparency within the FDA and drawn-out approval process appear to be hurting these businesses and resulting in job losses. I am sure our witnesses today are going to comment on that.

This is a very good hearing, Mr. Chairman. I appreciate you and Chairman Upton for holding it. I look forward to hearing from our witnesses.

With that, I would yield to whoever I should yield to.

I yield back to the Chair.

Mr. PITTS. Thank you.

The Chair recognizes the ranking member, Mr. Pallone, for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts.

I am pleased that you scheduled hearing today's hearing on medical devices because I believe we are at an important crossroads. As we continue to work our way out of the recession toward a thriving economy that offers economic opportunities to all Americans, we must out-innovate the rest of the world. America's competitiveness depends on our ability to innovate and keep America number one. However, to do that we must properly fund key agencies like the FDA that are essential to assisting in the development of new drugs and devices; and I am disappointed in the cuts proposed by the House Republicans.

Research and development has an impact on all sectors of our workforce. I will use my home State of New Jersey as an example. A new report by Research America noted that New Jersey is the third-largest R&D employer in the U.S., with more than 211,000 jobs supported by health R&D, including 50,000 direct jobs in health R&D. The same report shows the economic impact in New Jersey is $60 billion.

That said, the government must be responsible for facilitating an environment where Americans can continue to innovate. That is the key to creating new, thriving industries that will produce millions of good jobs here at home and a better future for the next generation.

If government abandons its role, we run the real risk of squandering too many opportunities that lead to innovative discoveries and great economic benefits.

Now, I have been interested in today's topic of FDA regulation for a long time, and that includes examining where the current system works well and where shortfalls might be. During this time, I have heard from patients, from physicians, and from companies about problems with the 501(k) process. Physicians and patients are concerned that products aren't fully evaluated before they are allowed on the market, and companies are frustrated of the lack of predictability and transparency in the process.

In fact, as chairman of the subcommittee, we held a hearing on these issues in 2009; and, during that hearing, we specifically heard about a GAO report on the 501(k) process and in particular on the pre-amendment devices that have never been through the FDA approval process. The FDA is here today, and I hope we can hear about their progress with reviewing the high-risk Class III devices that have yet to ever be approved formally.

I am also interested to hear about FDA's recently released innovation initiative, because I strongly believe the FDA has two very important parts to its mission—first, to make sure that products are safe for U.S. consumers and, second, to facilitate innovation. It is good to see FDA's renewed focus on the latter, and I look forward to the Institute of Medicine, or IOM, analysis of some of their recommendations.

Let me close by saying that today we will likely hear about two very different studies that have come to two very different conclusions, each with merit and limitations. In my view, this showcases one more reason why the upcoming IOM report due out in June is so critical to this dialogue.

I look forward to our witnesses' testimony. I hope that our discussion will inform both Congress and the FDA how to approach these issues in a balanced way, protecting the American consumer while maintaining a strong R&D basis in this country.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and yields to the chairman of the full committee, Mr. Upton, for an opening statement.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Thank you, Mr. Chairman, for holding today's hearing on the impact of medical device regulations on jobs and patients. We do need to get America back to work; and, as we talked about on the House floor last week, part of this involves fixing regulatory problems caused by the Federal Government.

Our Nation has been the world leader on medical devices, using American innovation to bring life-saving, life-improving devices to American patients and create high-paying, rewarding jobs here at home. In 2008, the medical device industry directory employed over 420,000 Americans. In my home State of Michigan, over 9,000.

Unfortunately, our world leadership is being threatened. As Chairman Pitts outlined so well last week on the House floor, it does appear that a major reason for this is a lack of predictability, certainty, and transparency at FDA. These problems at the FDA are hurting American innovation, costing American jobs, and hurting American patients.

According to recent reports and firsthand accounts from our Nation's small businesses, device companies are being forced to market their devices first in Europe because the EU countries have predictable and consistent regulatory processes. Because of that, medical devices are available there 2 years ahead of folks here. That is not right. This hearing aims to try and fix that.

I yield back my time.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Thank you for holding today's hearing on the impact of medical device regulation on jobs and patients. I also would like to thank the witnesses for testifying today on this important subject.

We need to get Americans back to work. As we talked about on the House floor last week, part of that involves fixing regulatory problems caused by the federal government.

Our Nation has been the world leader on medical devices, using American innovation to bring life-saving, life-improving devices to American patients and create high-paying, rewarding jobs here at home.

Unfortunately, our world leadership is being threatened due in part to the lack of predictability, certainty and transparency at the Food and Drug Administration. These problems at FDA are hurting American innovation, costing American jobs and hurting American patients.

The Medical Device User Fee Act expires in September of 2012, and this Committee will be charged with leading its reauthorization. I commit here today that this Committee will work hard to accomplish this reauthorization, but in doing so, we will demand that certainty, predictability and transparency be built into our process so our nation can stay as the global leader in medical device innovation, so we can create good-paying jobs here at home, and so we can improve the lives of patients.

It is time to get Americans back to work, and I thank the Chairman for holding this hearing so we can identify ways to do just that. I yield back.

Mr. PITTS. The chair yields to Dr. Burgess to continue your time.

Dr. BURGESS. Thank you, Mr. Chairman.

I certainly hear from device manufacturers all across the country about the lack of transparency and an ambiguous and constantly changing approval process that discourages innovation and ultimately does yield to the loss of American jobs. The inability to facilitate a predictable process is causing device manufacturers to move overseas and, most importantly, not allowing patients access to treatments here in the United States that have been found elsewhere.

The difficulty by the FDA to ensure reliable and consistent approval process not only creates a disadvantage for current devices, but it is an inhibitory environment on advances in technology in the future.

Earlier this week, Dr. Francis Collins, Director of the NIH, came and addressed a few of us at the Health Caucus. He talked about the changes that are occurring with genetic mapping and the new information that is coming online very rapidly. And this whole era of rapid learning can in fact lead to a multiplier effect in the development of many interventions that were never before imagined.

Investment, yes. Congress does need to make an investment. But also the integration of information is going to be critical in the development of new interventions, and the FDA is the lynchpin in all of that.

Certainly the National Institute of Health and the Center for Medicare and Medicaid Services need to be discussing with each other about future treatments that are going to be necessary and how to integrate those into the payment system. But if the pipeline is not unclogged at the FDA, then many of these new promises are never going to be kept.

Now, President Obama talked in the State of the Union address and advocated for America to lead the way in technology and innovation. Unfortunately, his signature health care legislation passed less than a year ago, coupled with the Food and Drug Administra-

tion's confusing and sometimes disjointed approval process, has instead encouraged the offshoring of business that has brought medical discoveries to a halt.

And let me yield the remaining time to the gentleman from New Jersey, Mr. Lance.

Mr. LANCE. Thank you very much for yielding; and thank you, Mr. Chairman.

The medical device industry produces $135 billion in products and employs at least 422,000 residents of this country. In New Jersey, over 20,000 employees in the medical device industry produce nearly $6 billion in products. Many are employed at incubator companies that develop new devices.

While the United States remains the leader in innovation in the medical device industry, that place is not set in stone. As the chairman has indicated, a recent study found that the U.S. is slipping as other nations are gaining. Unpredictable, inefficient, and expensive regulatory processes are jeopardizing America's leadership position in medical technology innovation.

I look forward to hearing from the panel on ways we can improve the regulatory environment to strengthen our position as the global leader in medical technology.

Thank you very much, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and yields to the ranking member of the full committee, Mr. Waxman, for 5 minutes.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Chairman Pitts, for holding this important hearing today.

Let me start off with a couple of statements on which I think we all can agree. We all want to ensure that innovation in the medical device industry is vibrant and healthy so that we have access to the best and newest technological advances. We also want the medical devices we use to be as safe as possible and to have every confidence that they are effective. If there are factors that are preventing or inhibiting these things from occurring, we should all be united in doing whatever it takes to reverse these influences.

But we cannot have a conversation about innovation and speeding new devices to the market without talking about the importance of ensuring the safety and effectiveness of those devices. So this hearing should be about how we can work together to meet these goals.

We will hear today from witnesses invited by the Republicans who will express their concern that the FDA's device regulatory system is inhibiting innovation, depriving patients of new and potentially life-saving devices, and costing American's jobs.

To focus on the other end of the equation, we have also invited two witnesses who will focus on FDA's responsibility to ensure the safety and effectiveness of devices; and we are also fortunate to have the FDA itself here to respond to concerns on both issues.

We shouldn't be Democrats on one side of this issue and Republicans on the other. We should all be together and carefully exploring the concerns about the state of innovation of the device indus-

try. It is important we ask some hard questions about the facts and data underlying these decisions.

Although Dr. Makower's study, for instance, raises some important questions, it is also clear there are some significant limitations. So what it tells us about what is actually going on according to the study itself, it includes a very small portion of the device industry—only 204 out of some 16,000 companies registered with the FDA. It also includes a majority of responses from companies that appear to have had very little previous experience with the FDA's regulatory process.

The study asserts that it takes much longer for devices to reach the market as compared to the EU. Obviously, we would all be concerned if that was the case. But we need to make our judgements based on good data. I think there are some real questions about whether Dr. Makower's study demonstrates that these EU versus U.S. time differentials even exist and whether Dr. Makower's study was comparing equivalent measures for times to market. I look forward to hearing from our witnesses on these points.

I will also look forward to hearing from our witnesses about the need to assure that devices are safe and effective when they reach the market. There are countless and often tragic stories of patients injured, even killed, by unsafe devices. The study that Dr. Nissen will describe today shows that many devices that were recalled for serious safety reasons were not reviewed by FDA under the more stringent premarket approval, or PMA, process. That has got to be a concern. We need to ask why so many unsafe devices ultimately harm patients and explore what can be done to prevent injuries in the future.

In order to have a flourishing and innovative American device industry that puts safe and effective devices on the market, we need to have a strong and well-resourced FDA that is in the best interest of American patients but it is also in the interest of the device industry itself. If patients lose confidence in the FDA, they will lose confidence in industry as well.

This is an issue that can and should be bipartisan. I look forward to hearing from our witnesses today and to working with my colleagues on this matter.

Let me point out, Mr. Chairman, I wasn't aware of the fact that FDA was put in as just one of the members of this panel. I think if anybody is coming to testify from the administration, we have a long tradition of giving them a separate panel. And I know FDA agreed to testify here today. Had I been aware of it, I would have objected, because I think this is a very bad precedent. But we will go along with what has been agreed to for today, but I want it understood that this should be an exception, not the rule.

FDA particularly should be the focus of a lot of our inquiry. Is there a culture at FDA where they are slowing things down? Or is it a fact that they don't have enough resources? It is ironic that on the House floor today we are voting on a budget that will cut FDA—cut a lot of other things—but cut FDA.

So it is a little bit insincere when members talk about wanting to get more drugs and devices approved so that the consumers can get the benefits of the innovation, but, at the same time, we cut FDA to make it more difficult for them to accomplish that goal.

Thank you, Mr. Chairman. Yield back my time.

Mr. PITTS. The chair thanks the gentleman.

There is a vote on the floor, so we will recess until as soon as possible after the last votes, about 10 minutes after the last votes, and we will reconvene at that time.

The committee stands in recess.

[Recess.]

[Additional statements for the record follow:]

PREPARED STATEMENT OF HON. JOHN D. DINGELL

Thank you Mr. Chairman.

Today's hearing focuses on a very important topic—the impact regulation has on the development and approval of medical devices in the U.S., as well as the impact these regulations have on job creation and patient access.

In his State of the Union President Obama called on the need for government and business to work together "to out-educate, out-innovate, and out-build the rest of the world." This is a lofty goal, and a needed goal. Our peers in China, Japan, and India are hungry and motivated to be the leaders in the fields of education, science, and technological development—such as in the medical device field.

Yet I would ask my colleagues this very important question, how can we out-innovate our neighbors when the proposed CR we are voting on this week cuts the FDA's funding by roughly 10 percent—or $220 million. Our major research institutions will also see massive cuts—the NIH will see a cut of over $1 billion, the NSF will see a cut of $359 million and the Department of Energy Office of Science will see a cut of $893 million. How can our country out-innovate our competitors when we are blindly slashing the budgets of our country's research engines?

As my colleagues know, I have been raising concerns for years about the state of funding at the FDA. I find it curious that some of my colleagues who express concern about the speed with which medical products are approved in this country are prepared to vote to cut funding for the agency responsible for approving drugs and devices—an agency that has been systematically starved of resources over decades.

Many of my colleagues have also voiced strong opposition to user fees, and increasing these user fees. I would ask these colleagues, if you will not increase funding for FDA to hire the necessary personnel to improve the medical device process, and you will not support a user fee to improve the process, how do you expect our country to compete with China and Brazil and India?

I hope today will be an opportunity for all Members of the Committee to learn how very important resources are—financial and personnel—to the FDA's ability to fulfill its mission. More importantly, this hearing will allow us to begin to consider how best we can help our businesses work with FDA to accomplish both of their needs—the development of successful, safe and effective devices.

I look forward to hearing from our witnesses and I thank you for your time.

PREPARED STATEMENT OF HON. EDOLPHUS TOWNS

Mr. Chairman, Ranking Member Pallone, thank you for holding this important hearing on the impact of medical device regulations on jobs and on patients.

Let me start out by saying that I am glad to see that we are holding a hearing on job creation. This is what the American people want to see, and it is what people in my district really want to see.

I think it is important that while we consider regulations that impact companies, we should take a balanced approach and consider the impact these regulations have on patients. We need to do what we can to speed innovative products to the market, while ensuring that these products are safe. These devices range in risk—from low-risk products like tongue-depressors to high-risk products like aortic stints. It would be devastating to patients and their families for a defective or unsafe high-risk product to be sped to market.

I understand the criticism surrounding the regulatory process, but certain safeguards simply must be maintained in order to protect the public. Around 98% of medical devices each year are approved through the 501(k) process by the FDA, yet these devices rarely undergo any testing in patients, and manufacturing facilities are not subject to FDA inspections. Partially because of this, we have seen recent examples of withdrawals of medical devices such as implantable defibrillators that

have frequently failed and resulted in inappropriate shocks or failure to function during cardiac arrest. Similarly, automated external defibrillators (AEDs) were approved

under the 501(k) process, which have resulted in over 28,000 reports to the FDA of AED failures, and hundreds of deaths.

A serious review of the safety of these devices may have prevented patients and their families from undergoing unnecessary suffering.

It is clear that the review process by which FDA approves medical devices is in need of updated; however, let us not forget the serious public safety implications involved as we examine what needs to be done.

Thank you, Mr. Chairman. I yield the balance of my time.

Mr. PITTS. The hearing will reconvene with apologies to our witnesses.

We have a panel of six. Let me introduce the witnesses.

Dr. Jeff Shuren is the Director of the Food and Drug Administration's Center for Devices and Radiological Health. Dr. Joshua Makower is a Consulting Professor of Medicine at Stanford University. He is also the CEO of ExploraMed Development and a venture partnership at New Enterprise Associates. Mark Deem is the Managing Partner and Chief Technology Partner of The Foundry. Dr. Rita Redberg is the Director of Women's Cardiovascular Services and Professor of Medicine at the University of California, San Francisco Medical Center. Dr. Steve Nissen is a Professor of Medicine at the Cleveland Clinic Lerner School of Medicine and Chairman of the Department of Cardiovascular Medicine of the Cleveland Clinic Foundation. And Mr. Ralph Hall is a Distinguished Professor and Practitioner of Law at the University of Minnesota Law School. Without objection, your written statements will be inserted into the record. We will ask the witnesses to summarize their testimony into 5 minutes.

At this time, we will recognize Dr. Shuren for 5 minutes.

STATEMENTS OF JEFFREY E. SHUREN, M.D., J.D., DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION; JOSHUA MAKOWER, M.D., EXPLORAMED DEVELOPMENT, LLC; MARK DEEM, MANAGING PARTNER AND CHIEF TECHNOLOGY PARTNER, THE FOUNDRY; RITA REDBERG, M.D., MSC., DIRECTOR, WOMEN'S CARDIOVASCULAR SERVICES, UCSF MEDICAL CENTER DIVISION OF CARDIOLOGY; STEVEN E. NISSEN, M.D., PROFESSOR OF MEDICINE, CLEVELAND CLINIC LERNER SCHOOL OF MEDICINE AT CASE WESTERN RESERVE UNIVERSITY, AND CHAIRMAN, DEPARTMENT OF CARDIOVASCULAR MEDICINE, CLEVELAND CLINIC FOUNDATION; AND RALPH HALL, DISTINGUISHED PROFESSOR AND PRACTITIONER, UNIVERSITY OF MINNESOTA LAW SCHOOL

STATEMENT OF JEFFREY E. SHUREN, M.D.

Dr. SHUREN. Mr. Chairman and members of the subcommittee, I am Dr. Jeff Shuren, Director of the Center for Devices and Radiological Health at the Food and Drug Administration. Thank you for the opportunity to testify today.

Over the past decade, most indicators in medical device industry success have gone steadily upwards. From 2005 to 2009, the industry has added over 45,000 jobs, according to U.S. census data. It is one of the few U.S. manufacturing segments with a positive

trade balance. An especially crucial indicator is the attractiveness of an industry to capital investors and entrepreneurs. In 2010, the medical device industry was fourth in attracting venture capital investment, up from 13th place 10 years ago.

Although the medical device industry has weathered the recession far better than most of our industries, the economic climate has had an impact, with some companies choosing to move overseas. And as recent reports note, the recession has also caused companies to change their business models to be more risk averse and therefore more sensitive to FDA regulatory uncertainties.

We recognize that smart FDA regulation is critical to maintain U.S. competitiveness. Some would say that, despite the record of growth and prosperity in the U.S. device industry, the European regulatory system is better for industry and patients. It is difficult to make direct comparisons between the U.S. and European systems, given their fundamental differences, including, at the most basic level, differing approval standards.

The EU lacks the requirement in U.S. law that devices be shown effective. Device manufacturers in Europe select from a list of private companies for safety reviews and pay the chosen company for that review. The result is a European review process that does not have adequate public accountability, consistency, and transparency and is thus almost impossible to compare directly with FDA's.

This is in part why the European Commission has proposed that the EU regulatory framework be strengthened to better meet European public health expectations and to make European industry more competitive globally.

Our data reported to this committee just last week shows that, in fact, FDA's device review performance has been consistently strong; and even an industry funded study released just today shows we are beating the Europeans in the review time for lower risk and are in a tie for higher risk 501(k) devices.

Perhaps the more important consideration vis-a-vis Europe, however, is our comparative safety records. As a recent industry funded study pointed out, the absence of a centralized public database that captures all EU recalls and approvals makes it impossible to accurately compare recall rates in the EU and the U.S., and yet that study shows that 85 percent of safety reports come from only 5 out of the 24 European countries examined, suggesting there is a significant underreporting of safety problems by some EU countries.

In addition, that same study claims that both devices come on the market earlier in the EU and that recalls of specific devices in the EU and U.S. tend to occur within a few weeks of each other. If that were true, it would suggest that the EU takes longer to identify problems, exposing patients there to unsafe devices for a longer period of time.

In just the past few months, a surgical sealant and a form of breast implants were determined to be dangerous and pulled from the market after being approved under the EU system and used in thousands of patients. The result was surgical removal and patient suffering. Neither of these products were sold in the U.S.

Previously, other devices approved in Europe and not in the U.S. were pulled from the European market due to safety problems, in some cases, problems first identified in studies required by the

FDA to support approval for U.S. patients. If those products had been approved here, I have no doubt we would be having a different hearing today.

FDA has a responsibility to facilitate device innovation while assuring that devices are safe and effective. The comprehensive reports we released in August of last year showed that we have not done as good a job managing our premarket programs as we should. We have new reviewers who need better training.

We need to improve management oversight and standard operating procedures. We need to provide greater clarity for our staff and for industry about key parts of the 501(k) program. We need to provide greater clarity for industry about what we need from them to facilitate more efficient, predictable reviews. We need to find the means to handle the ever-increasing workload and reduce staff and manager turnover, which is almost double that in the drug and biologic centers.

We need to meet all of these challenges to improve predictability, consistency, and transparency in premarket review programs.

In January of this year, after extensive public input, we announced 25 specific actions we are taking this year to ensure that our premarket review programs both foster innovation and assure the safety and efficacy of medical devices for American patients. And just last week Commissioner Hamburg and I proposed the Innovation Initiative to accelerate the development and evaluation of innovative medical devices and strengthen the Nation's research infrastructure for developing breakthrough technologies in advancing regulatory science.

Mr. Chairman, I commend the subcommittee's efforts; and I am pleased to answer any questions the committee may have.

[The prepared statement of Dr. Shuren follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

JEFFREY SHUREN, M.D., J.D.

DIRECTOR

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U. S. HOUSE OF REPRESENTATIVES

"IMPACT OF MEDICAL DEVICE REGULATION ON JOBS AND PATIENTS"

FEBRUARY 17, 2011

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Jeffrey Shuren, Director 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 effects of medical device regulation on jobs and patients. FDA recognizes the many important contributions that the medical device industry makes to the economy and to the public health. By increasing the predictability, consistency, and transparency of our regulatory pathways, we can help provide better treatments and diagnostics to patients more quickly, stimulate investment in and development of promising new technologies to meet critical public health needs, and increase the global market position of U.S. medical devices.

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. Medical devices are assigned to one of three regulatory classes based on risk.

Class I, General Controls, is the lowest risk category of devices and includes items such as adhesive bandages. These devices are subject to the general controls of the Act, which include establishment registration and device listing, compliance with current Good Manufacturing Practice (cGMP) and labeling, record-keeping, and reporting requirements.

Class II, Special Controls, is a medium-risk category of devices and includes devices such as intravenous catheters and powered wheelchairs. They are subject to the general controls of the Act as well as Special Controls, which may include special labeling requirements, mandatory performance standards, and post-market surveillance, in order to ensure device safety and effectiveness.

Class III is the highest risk category of devices and includes devices such as heart valves and coronary stents. These devices are subject to the general controls of the Act, plus approval prior to marketing of a premarket approval application (PMA) containing scientific evidence of the device's safety and effectiveness.

Most devices, however, are cleared via the premarket notification [510(k)] process. A 510(k) is a premarket submission to demonstrate that the device to be marketed is "substantially equivalent" to another legally marketed (predicate) device. If a device

otherwise subject to premarket review is not substantially equivalent to another legally marketed device, it must go through either the PMA process or the "de novo" classification process (a review process for innovative, lower-risk products).

The Impact of Regulation on Innovation

FDA is charged with a significant task: to protect and promote the health of the American public. To succeed in that mission, we must ensure the safety and effectiveness of the medical products that Americans rely on every day, and also facilitate the scientific innovations that make these products safer, more effective, and more affordable.

These dual roles have a profound effect on the nation's economy. FDA medical device approval gives manufacturers a worldwide base of consumer confidence. Our ability to work with innovators to translate discoveries into approvable products in a timely way is essential to the growth of the medical products industry and the jobs it creates. U.S.-based companies dominate the roughly $350 billion global medical device industry. The U.S. medical device industry is one of the few sectors, in these challenging economic times, with a positive trade balance.[1] In 2000, the U.S. medical device industry ranked thirteenth in venture capital investment – now, ten years later, it's our country's fourth largest sector for venture capital investment.[2]

[1] PwC (formerly PricewaterhouseCoopers), "Medical Technology Innovation Scorecard" (January 2011) at page 8, available at http://pwchealth.com/cgi-local/hregister.cgi?link=reg/innovation-scorecard.pdf.
[2] PricewaterhouseCoopers/National Venture Capital Association, MoneyTree™ Report, Data: Thomson Reuters, Investments by Industry Q1 1995 - Q4 2010, available at http://www.nvca.org/.

As noted in a January 2011 report on medical technology innovation by PwC (formerly PricewaterhouseCoopers), the U.S. regulatory system and U.S. regulatory standard have served American industry and patients well. As that report states, "U.S. success in medical technology during recent decades stems partially from global leadership of the U.S. Food and Drug Administration. FDA's standards and guidelines to ensure safety and efficacy have instilled confidence in the industry's products worldwide. Other countries' regulators often wait to see FDA's position before acting on medical technology applications, and often model their own regulatory approach on FDA's."

Some have alleged that delays in FDA approval deprive American patients of needed therapies and push jobs overseas. Yet, as FDA's FY2010 Medical Device User Fee Act Performance Report to Congress indicates, FDA's device review performance has been consistently strong. Ninety-five 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 in total) 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 by 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 proposed indications for use. 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.

Comparisons Between FDA and the European Union (EU)

As FDA and industry have geared up to negotiate a new user fee agreement under MDUFA, we've seen reports and studies comparing FDA and EU device review performance, with some suggesting that we replace the American system with that of the EU. It is important to note that there are some very basic differences between the two systems that confound comparisons. In contrast to the U.S. medical device regulatory system, the European system:

- does not require government review before a company may market a device;
- does not require demonstration of device effectiveness – the U.S. standard in law is safety and effectiveness; the EU standard is safety and performance, meaning the device must perform as indicated in the device description and is not required to show benefit to the patient;
- allows manufacturers to "forum-shop" their applications among third-party reviewers who are subject to minimal oversight;
- provides minimal information to the public about the evidence supporting company claims; for example, summaries describing the basis for third-party reviewer decisions to grant a CE mark are not provided to the public;
- has no centralized authority for tracking safety information related to medical devices and no EU-wide post-market surveillance system; as a result, the EU is less likely to detect new safety problems as compared to the United States; and
- has no centralized database of information about the performance of the various regulatory systems (such as time spent on premarket review), making it difficult to compare the performance of the EU and U.S. systems.

In 2008, the European Commission acknowledged that there were limitations in its regulatory framework for medical devices and sought public comment on ways to

strengthen its system.[3] As noted by the Commission in its Public Consultation Report: "Experience indicates that the current system does not always offer a uniform level of protection of public health in the European Union. New and emerging technologies have challenged the current framework, highlighting gaps and pointing to a certain scarcity of expertise.... And finally, the legal system has been criticized as being too fragmented and difficult to follow and fraught with national variation."[4]

Different studies report different time frames for U.S. and EU review times for new medical devices, for a variety of reasons. Comparisons of review times between the United States and the EU are particularly difficult when based on flawed assumptions and in the absence of performance data for the EU. For example, the widely cited Makower study, which concluded there was a significant lag in "review times" in the United States as compared to the EU, included within the "review time" the substantial pre-submission assistance to the industry that FDA offers.

For the most complex devices, FDA reviews may indeed take longer from our first contact with a company to approval – in large part, due to our agreement with manufacturers to engage with them far earlier in the product development process than do our European counterparts. Of note, the number of such meetings requested by manufacturers has been steadily increasing over the past few years.

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[3] European Commission, "Recast of the Medical Devices Directives: Public Consultation," available at http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/public_consultation_en.pdf; see generally http://ec.europa.eu/consumers/sectors/medical-devices/documents/revision/index_en.htm.
[4] European Commission, Consumer Affairs, "Revision of the Medical Devices Directives: 2008 - onwards," at http://ec.europa.eu/consumers/sectors/medical-devices/documents/revision/index_en.htm.

An additional factor is that for the higher-risk devices, FDA may ask for more robust clinical data to meet the stronger U.S. regulatory standards. As noted previously, FDA requires a manufacturer to demonstrate that a device is safe and effective, while the European process only requires a demonstration of a device's safety and performance, not its effectiveness. For example, if a manufacturer wishes to market a laser to incise heart tissue to treat arrhythmia (abnormal heart rhythm) in the EU, the manufacturer must show that the laser incises heart tissue only. In the U.S., however, the manufacturer must show that the laser incises heart tissue and also treats the arrhythmia.

Comparisons of safety data are equally problematic. Since the number of approval submissions or "on-market" devices in the EU cannot be determined from publicly available information – nor can the number of recalls or adverse event reports – calculation of accurate rates of safety problems is not possible. According to the industry-funded BCG study on EU and U.S. recalls, 85 percent of medical device safety reports in the EU come from only five member states of the 24 countries reviewed, underscoring the potential for underreporting of safety events in the EU.

We appreciate the concern that some devices come on the market in the EU before they do in the United States. While we want devices to be available to American patients as soon as possible, we believe that, consistent with U.S. law, they need to be both safe and effective. The U.S. system has served patients well by preventing EU-approved devices that were later shown to be unsafe or ineffective from harming American consumers. For example, in 1991, Poly Implant Prosthese (PIP), a company based in southern France,

received a CE mark for silicone breast implants. Unbeknownst to regulators, PIP changed the silicone gel in the breast implants. On March 30, 2010, French regulators issued a recall of all pre-filled silicone breast implants manufactured by PIP. The breast implant recall is said to affect an estimated 35,000 to 45,000 women worldwide. This device was never approved by FDA and therefore never reached the market in the United States.

Yet, FDA recognizes that it can do a better job at managing its premarket review programs. FDA continues to look for ways to improve our ability to encourage innovation and to speed safe and effective products to patients. We know that medical device development is expensive. And we agree that, in many areas, insufficient clarity, consistency, and predictability on our part contributes to those expenses. This is why we've undertaken initiatives to improve our review processes in order to enhance innovation in the medical device industry.

510(k) Action Plan

In recent years, concerns have been raised, both within and outside of FDA, about whether the current 510(k) program optimally achieves its goals of fostering innovation while making safe and effective medical devices available to patients. 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.

Under the first part of this assessment, FDA created 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 recommends how it can do so more predictably. The other part of this assessment is an independent evaluation by the Institute of Medicine (IOM), which is still underway. The IOM is expected to publish its final report in summer 2011.

In keeping with our commitment to transparency, FDA sought public input during the development and review of the two internal reports. We engaged in extensive public outreach, including two public meetings, three town hall meetings, three public dockets and many smaller meetings with a variety of stakeholder groups. In August 2010, FDA issued final reports containing 55 recommendations and again sought public comment on the reports and recommendations before taking action.

In January 2011, after reviewing the public comment, the Agency announced the actions it would take to improve the 510(k) process and its use of science in decision-making generally. In particular, these actions are intended to improve the predictability, consistency, and transparency of the 510(k) program and aspects of our PMA program, such as decisions regarding clinical trial protocols to facilitate innovation while assuring that devices available to patients are safe and effective. A few examples include:

- Streamlining the review process for innovative, lower-risk products, called the "de novo" classification process;
- Publishing guidance for industry to clarify when clinical data should be submitted to increase predictability and transparency;
- Developing a network of external experts who can use their knowledge and experience to help the Agency address important scientific issues regarding new medical device technologies; and
- Establishing a new Center Science Council of senior FDA experts within the Agency's medical device center to ensure more timely and consistent science-based decision-making.

Innovation Pathway

In addition to our review of the 510(k) program, we recently announced a priority review program for new, breakthrough medical devices. The proposed new Innovation Pathway program for pioneering medical devices is part of a broader effort we have underway designed to encourage cutting-edge technologies among medical device manufacturers.

The Innovation Pathway will seek to accelerate the development and regulatory evaluation of innovative medical devices, strengthen the nation's research infrastructure for developing breakthrough technologies, and advancing quality regulatory science. As part of this initiative, CDRH 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; and
- Engaging in formal horizon scanning – the systematic monitoring of medical literature and scientific funding to predict where technology is heading, in order to prepare for and respond to transformative, innovative technologies and scientific breakthroughs.

Facilitating medical device innovation is a top priority for FDA. As part of its 2011 Strategic Plan, FDA's medical device center set goals to proactively facilitate innovation to address unmet public health needs. A public docket has been set up to solicit public comment on the Innovation Pathway proposals, and a public meeting on the topic is scheduled for March 15, 2011.

MDUFA Reauthorization

As you know, the statutory authority for MDUFA expires on September 30, 2012. At that time, new legislation will be required for FDA to continue collecting user fees for the medical device program. FDA is currently engaged in negotiations with the regulated industry to prepare recommendations for the reauthorization of MDUFA. In addition, the Agency is holding regular monthly discussions with representatives of patient and consumer advocacy groups, while the negotiations with industry are taking place, as required by the statute. Minutes of both the industry negotiations and the monthly stakeholder meetings are being made publicly available on the FDA website to ensure transparency of the reauthorization process and to facilitate stakeholder involvement in that process. Finally, FDA will hold a public meeting on MDUFA reauthorization later this year.

Issues of concern to industry will appropriately be addressed in these negotiations, and during this process, all other stakeholders – including the scientific and medical community, and patient and consumer groups – will be afforded the opportunity to make their views heard with respect to the reauthorization of MDUFA.

We look forward to working with Members of the Committee on Energy and Commerce to reauthorize this important legislation.

CONCLUSION

Mr. Chairman, I commend the Subcommittee's efforts to understand the impact of FDA's regulatory policies on medical device innovation. FDA strives toward a reasonable and fair approach to regulation that will foster innovation in the medical technology industry while assuring that the medical devices marketed in the United States are safe and effective. Thank you for your commitment to the mission of FDA, and the continued success of our medical device program, which helps get safe and effective technology to patients and practitioners on a daily basis.

Mr. Chairman, that concludes my formal remarks. I will be pleased to answer any questions the Subcommittee may have.

Mr. PITTS. The chair thanks the gentleman and recognizes Dr. Makower for 5 minutes.

STATEMENT OF JOSHUA MAKOWER, M.D.

Dr. MAKOWER. Thank you, Chairman Pitts, Ranking Member Pallone, members of the subcommittee. Thank you for the opportunity to testify today.

My name is Josh Makower, and I have dedicated the past 22 years of my life to developing therapies and technologies to improve patient care. Over this time I have founded six independent medical device companies which have created several hundred jobs and touched the lives of hundreds of thousands of patients worldwide.

In addition to being a physician, inventor and entrepreneur, I cofounded the Stanford Biodesign Innovation Program to teach the process of medical innovation to the next generation of innovators.

I am here today because I am deeply concerned that we are in jeopardy of losing U.S. leadership position in medical technology innovation as a result of the current regulatory environment at FDA. Over the past few years, it has been increasingly more difficult, more time consuming, more costly, and less predictable to navigate the FDA. As a result, investment is drying up, companies are moving overseas or closing their doors, and U.S. patients are being denied timely access to safe and effective new medical products. If this situation does not improve immediately, a generation of innovation businesses will be lost, along with the jobs they would have created and the lives they would have saved or improved.

These are not my concerns alone. Numerous studies and reports over the past year document the difficulty innovators are having navigating the FDA.

In response to questions from Members of Congress and FDA officials regarding the scope of the problems, I, along with several colleagues from Stanford, conducted a survey of over 200 medical technology companies to generate data on their specific experiences. So much of what has become policy over the past few years has been based on anecdote and singular examples, and I felt compelled to bring data to this discussion. It is essential we use data to drive our decision making. Recognizing that all studies have limitation, mine is no different. However, the results of my study are compelling and justifiably cannot be ignored or dismissed.

I have submitted the results of the full survey as part of my testimony but want to briefly point out some of the most significant findings.

Most notably, the survey found that, on average, innovative new medical devices are available to U.S. Citizens 2 full years later than patients in other countries. In some cases, American patients wait as long as 6 years, longer than patients elsewhere for American-made technology. This hurts patients' health and U.S. competitiveness.

There is no other way to say this. Today, American innovation, investment, and manufacturing in medical technologies are leaving this country and landing in Europe, Asia, and elsewhere first. These findings don't only have negative repercussions for patients. They hurt job creation in this country.

The most innovative products being designed today are really made by small and mid-sized companies. These are the very innovators that the President and Congress have called upon to lead us out of our economic challenges, but they are starving for funding, and they are running out of time. They are being crushed with overly burdensome regulation; and now, with the medical device tax, they are being taxed before they ever become profitable. This is wrong, and we cannot let it continue.

We all know we need an FDA. Their mission to protect and promote the public health is a good one. We all want products that have a reasonable assurance of safety and efficacy, but we cannot make the process so difficult or so costly that we kill the very innovation we depend upon to advance the public health, the very innovation we depend upon to advance our economy.

Today, unfortunately, this industry is at a crossroads. Driven by high-profile anecdotes and a fear of making a mistake, our FDA has become more risk averse, while becoming less predictable, less reasonable than in any time in our history.

My colleagues and I who have spent our careers focused on patient care are now seeing foreign patients reaping the benefits of American ingenuity first before Americans ever get a chance to. We are seeing jobs move overseas; and, worse, we are seeing yet another one of America's great industries brought to its knees, struggling to survive under a system we created.

Let's work together to make sure that American patients and workers reap the benefits of these amazing medical advancements first. Let's work together to provide a predictable and reasonable regulatory environment for our Nation's med-tech entrepreneurs, and let's make sure that the generation of innovation is not lost forever. We owe this to the pioneering medical innovators who came before us, to our students, and the innovators of the future, to the men and women whose jobs rely upon us, and, most importantly, to the patients who depend upon us for their survival and their quality of life.

Thank you.

[The prepared statement of Dr. Makower follows:]

Testimony of Dr. Josh Makower

February 17, 2011

U.S. House of Representatives

Energy and Commerce Subcommittee on Health

Hearing: "Impact of Medical Device Regulation on Jobs and Patients"

Dr. Josh Makower Testimony

My name is Dr. Josh Makower and I have dedicated the past 22 years of my life to developing therapies and technologies to improve patient care. Over this time I've founded 6 independent medical device companies which have created several hundred jobs in the United States and the technologies I have invented and developed have touched the lives of hundreds of thousands of patients across the world. I am an inventor on over 100 issued patents and on over 330 patent applications. Through the medical device incubator, ExploraMed, that I started back in 1995, our medical device companies have developed technologies to address conditions such as coronary and vascular occlusion, heart failure, incontinence, osteoarthritis, chronic sinusitis, chronic and acute otitis media, obesity, prostatic disease, and several other major medical conditions. ExploraMed receives support from NEA, a venture fund, where I also serve as a Venture Partner on the Medical Device team. NEA has been helping to build great companies since 1978. In addition to being a physician-inventor and entrepreneur, I am a Consulting Professor of Medicine at Stanford University and have co-founded the Stanford Biodesign Innovation Program to teach the process medical technology innovation to the next generation of innovators. This effort has graduated hundreds of students through our fellowship and course programs and now includes Biodesign Innovation collaborations with leading universities across the globe.

My reason for being here today is that I care deeply about patients and patient care and understand how acutely important medical technology innovation is to the advancement of the health and well being of our society. I am also here today because I am deeply concerned that we are in jeopardy of losing the US leadership position in medical technology innovation as a result of the current regulatory environment at FDA. Over the past few years it has been increasingly more difficult, more time consuming, more costly and *less* predictable to navigate the FDA approval process. As a result, investment is drying up, companies are moving overseas or closing their doors and US patients are being denied timely access to safe and effective new medical products. If this situation does not improve immediately, a generation of innovation and businesses will be lost, along with the jobs they would have created and the lives they would have saved or improved.

These concerns are not mine alone. Numerous studies and reports over the past year document the difficulty innovators are having navigating the FDA. In response to questions from Members of Congress and FDA officials regarding the scope of the problems, I, along with Abeed Meer of Stanford, conducted a survey of over 200 medical technology companies to generate data on their specific experience. So much of what has been become policy over the past few years has been based on anecdotes and single examples and I felt compelled to bring data to this discussion. It is essential we use data to drive our decision-making. Recognizing that all studies have limitations, mine is no different; however, the results of my study are compelling and cannot be justifiably ignored or dismissed.

Before discussing the specific findings, it is important to have a better understanding of the medtech industry which plays an important role in the lives of patients around the world. In this context, medtech refers to medical devices intended for use for therapeutic and diagnostic

purposes. Together with other segments of the larger health care sector, medtech companies have contributed to dramatic improvements in health. For example, from 1980 to 2000, new diagnostic and treatment paradigms helped drive a 4 percent increase in life expectancy in the U.S., a 16 percent decrease in annual mortality rates, and a 25 percent decline in disability rates for the elderly.[1]

The U.S. medtech industry also has an essential role in the U.S. economy. In 2006, companies in the field shipped products valued at $123 billion and paid $21.5 billion in salaries.[2] The industry directly employs more than 400,000 employees, and is responsible for over 2 million total jobs, including those that support this vibrant industry. Employees in the medtech field earn above average wages—approximately $60,000 per year—because the industry requires and attracts a highly skilled and educated workforce.[3] New medical technologies also have the potential to drive down costs in a world of escalating healthcare expenditures.

Internationally, the U.S. is the largest global consumer of medical devices. However, it is also the world's leading producer. The country achieved this leadership position through decades of strong, sustained investments in research and development (R&D) by U.S. medical device companies and the venture capital community that backs them. As a result, the medtech field is among a limited number of industries in which the U.S. maintains a trade surplus. In 2007, the total medtech trade surplus was estimated at $5.4 billion.[4]

Traditionally, innovation in the medtech industry has been driven by small, entrepreneurial companies with a passion for discovering safer, more effective ways to diagnose and treat patients. Although a number of major device manufacturers exist, more than 80 percent of medtech companies have fewer than 50 employees.[5] These small starts-ups are the engine that fuels the development of innovative new devices, which are often acquired by the larger companies. Through the combined efforts of both small and large medtech companies alike, R&D investment in the industry more than doubled during the 1990s, and it continues to outpace the R&D investment of companies in other U.S. manufacturing industries by an average of twice as much.[6]

However, over the past few years, navigating the FDA has become less predictable, more time consuming and more costly. As a result, we are losing our global leadership position in medical technology innovation.

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[1] "The Value of Investment in Healthcare," MEDTAP International, 2004, www.aha.org/aha/content/**2004**/PowerPoint/**Value**Presentation.ppt (October 2, 2010).
[2] "State Economic Impact of the Medical Technology Industry," The Lewin Group, 2010, http://www.ihif.org/files/State%20Impacts%20of%20the%20Medical%20Technology%20Industry_%23436092%20_3_.pdf (October 26, 2010), p. 1.
[3] Ibid., p. 4.
[4] "Medical Technology and Venture Capital: A Fruitful Yet Fragile Ecosystem," MDMA and NVCA, June 2009, http://www.medicaldevices.org/node/656 (October 2, 2010).
[5] Ibid.
[5] "Medical Devices Industry Assessment," International Trade Administration, 2009, http://www.ita.doc.gov/td/health/Medical%20Device%20Industry%20Assessment%20FINAL%20II%203-24-10.pdf (October 2, 2010).

In fact, just last month, PwC issued an innovation scorecard on medical technology innovation, and the message was dire. PwC looked at several factors in innovative nations, including the availability of investment resources and efficiency of regulatory systems. The study showed that it is clear that American innovators are going outside the U.S. first to seek clinical data and revenue. While much of this innovation is finding its way to European patients, the study notes that by 2020, it is likely that other nations such as Brazil, India and China will benefit from America's regulatory challenges. Simply put, we have no time to lose.

The FDA

Within the FDA, CDRH has two primary regulatory pathways that medical devices can take to get to market. The Center uses the premarket approval (PMA) pathway to evaluate and approve technologies that are truly novel and pose a high potential risk to the patients using them. For low to medium risk devices, it employs the premarket notification or "510(k)" process. Regardless of whether a device must follow the 510(k) or PMA pathway, the FDA has the ability to request that a company provide clinical data to support clearance or approval. This data often requires an allowance by the FDA to perform clinical trials in the U.S., which is known as an investigational device exemption (IDE).

Early in the implementation of section 510(k) of the Medical Device Amendments, it was well recognized that the 510(k) pathway to market could efficiently facilitate the availability of new technologies that have the same intended use as legally marketed devices without creating an undue regulatory burden. This approach was intended to allow companies to build upon established clinical and scientific evidence of safety and effectiveness to more rapidly iterate and improve the innovations available to patients. Not surprisingly, the 510(k) process is more widely used than the PMA pathway. In 2009, for example, CDRH approved just 15 original PMA submissions while it cleared approximately 3,000 products under a 510(k).[7]

As it shepherds technologies through these two pathways, the FDA must balance the imperative of assuring the safety, effectiveness, and quality of commercially available medical devices with its mission of fostering innovation by providing companies with a timely, predictable route to market. In recent years, some politicians, members of the press, and consumer groups have criticized the FDA for not adequately addressing the safety of medical devices, particularly those cleared through the 510(k) pathway. These concerns have persisted despite a lack of evidence that both the 510(k) and PMA pathways are not fulfilling their intended purpose of protecting patients. In fact, despite the anecdotal examples reported in the media, there is compelling evidence to the contrary. For example, one recent study demonstrated that approximately 99.6 percent of all 510(k) and PMA devices that were cleared/approved by the FDA from 2004 to 2009 have not been associated with a Class I[8] recall.[9] (Recalls are an indicator of major device problems that have the potential to negatively affect patient safety and/or device effectiveness.) Such results demonstrate that serious device-related safety problems are extremely rare. Also,

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[7] Calculated from FDA data available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm and http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm (October 22, 2010).

[8] A Class I recall is the most serious type of FDA recall because the problem for which the device has been recalled may result in major injuries or death.

[9] Hall, op. cit.

the data shows that the majority of these rare postmarket events stem from issues relating to quality systems and manufacturing processes and not issues that would have been most effectively detected through more expansive premarket clinical trials.

Despite this evidence, the FDA's clinical data requirements continue to rise. While the agency historically used the postmarket period to continue accruing data regarding device safety and effectiveness (allowing the market to determine the value of a medical device), it is increasingly demanding that this kind of large-scale clinical data during the premarket period. When it comes to premarket data requests for new products, medtech innovators say they face more uncertainty regarding the FDA's expectations, and that bench, animal, and clinical testing requirements are mounting without clear justification or benefit. Even more troubling are an increasing number of examples from industry representatives that FDA reviewers have requested esoteric scientific testing, or posed questions that are not reasonably answerable, sometimes at great expense and with little relevance to safety and effectiveness. Moreover, medtech innovators have reported that the FDA is becoming less predictable and increasingly inefficient in its premarket review role. Stakeholders maintain that the CDRH, over the last several years, has become even less transparent in how it makes decisions, as well as slower in responding to inquiries and regulatory submissions. The degree to which these reports represent isolated incidents versus a general trend was unknown prior to the initiation of the study I conducted.

According to device companies, changes at FDA have created nearly insurmountable barriers to medtech innovation in the U.S., with no apparent off-setting public health benefit. The current regulatory environment is particularly challenging for start-up companies – which have historically played a key role in driving innovation – because of their limited financial resources. As a result, regulatory submissions and clearances/approvals for innovative new medical devices are declining in the U.S. In an era of greater scientific knowledge and technology advancements than any other time in history, one must question what forces are driving medical technology innovation in a downward direction.

The purpose of the study was to gather quantitative and qualitative data from a representative subset of medtech companies to elucidate the impact of the FDA's current regulatory practices on medical technology innovation and the advancement of public health so that Congress, the FDA, and the IOM would have more information to consider it in their evaluation.

I have submitted the full study as a part of my testimony, but I want to highlight several powerful findings.

The study found that for low- and moderate-risk devices, the process to navigate the FDA took companies up to two years longer than it did for a similar approval from European regulators. For higher-risk devices, the discrepancy was greater -- in the U.S. , it took three and a half years, or five times as long as Europe, to grant approval.

By overwhelming 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 were not present at meetings between the companies and FDA to discuss review issues.

Given that it takes longer and costs more money to launch a product in the US, a reasonable question is what is gained from the additional time and costs that result from the FDA process.

A recent study conducted by the Boston Consulting Group answered this question. The report examined the rate of safety recalls for medical devices in Europe from 2005-2009 and compared them with the level of similar recalls in the U.S. It found that there is little to no difference between average recall rates in the United States and the European Union. Essentially, American patients and workers are getting none of the upside to today's regulatory environment, but all of the downside.[10]

It should be noted that neither I, nor my colleagues, oppose FDA asking for clinical data when the circumstances warrant. In fact, FDA currently has the authority to ask for data whenever they deem it necessary. The problem for medical technology innovators arise when the requirements change at FDA without transparency or without justification. This uncertainty is harmful to innovation, job creation and patient care because it stymies future investment in medical technology innovation.

Another critical issue is the severe decrease in investment funding for innovative medtech companies. Series A financings are a leading indicator for innovation and job creation in the medical technology industry. Unfortunately, due to today's current regulatory environment, the number of start-ups receiving this crucial funding is down almost 50 percent from two years ago. According to a PwC/National Venture Capital Association report, in 2008, 118 start-ups received Series A funding, while in 2010, this number dropped to 60. In order for innovative companies to drive job-creation and patient care, this trend cannot continue.

Implications to the U.S. Economy

Until recently, device innovation has largely been a U.S. phenomenon—the most important new technologies were invented here, and commercializing them in the sizable U.S. market was at the core most medtech company strategies. However, as medtech hurdles have climbed and available funding has declined, device companies are considering alternative strategies that are less U.S.-dependent. Unfortunately, as described, this means that many new technologies are reaching U.S. patients later than patients in other geographies. It also suggests that the United States is at risk of losing its premier position at the center of the global medtech innovation ecosystem. As this epicenter shifts, the U.S. economy will be negatively impacted as jobs are moved overseas.

Despite the fact that U.S. elected officials are calling for increased innovation and the high-quality, high-salary jobs associated with innovative industries, survey respondents verified in their comments that medtech jobs are moving offshore. For instance, one participant reported that his device company had recently set up overseas operations, firing 19 employees in the U.S.

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[10] http://www.advamed.org/NR/rdonlyres/061A4AC8-D6A3-4960-826B-672214A0A623/0/REPORTBCGEuropeanUSSafetyFINAL.pdf

and hiring 12 in Europe. Next, the company planned to shut down its U.S. production facility and move another 30 to 40 manufacturing jobs to Europe. In this particular example, all future growth was also planned overseas. Keeping in mind that every direct medtech job is indirectly responsible for another 4.47 jobs in the national economy,[11] the effect on U.S. employment could be sizable.

While the needs of an industry or the economy at large should never be prioritized over patient safety, it is not clear that the current regulatory obstacles to U.S. market entry that are imposed on medical innovators truly contribute to the protection and promotion of public health. Given the dire economic condition of the U.S. at the present time, the trend toward creating exceptional barriers for one of the few remaining industries in which our country is still a leader should be a significant cause for concern.

Looking Forward

Our nation currently faces unprecedented challenges in almost every sector of the economy. However, to individual citizens, nothing is more important than their own health and welfare, as well as the health and welfare of their families. Regulators and innovators have an important responsibility to protect and advance public health, and to maintain the balance between risks and benefits for the patients they serve. In doing so, the patient must remain first and foremost in our minds at all times. Patients can be harmed if unsafe medical technologies reach the market, but they are also harmed when important innovations are not available to treat their medical conditions.

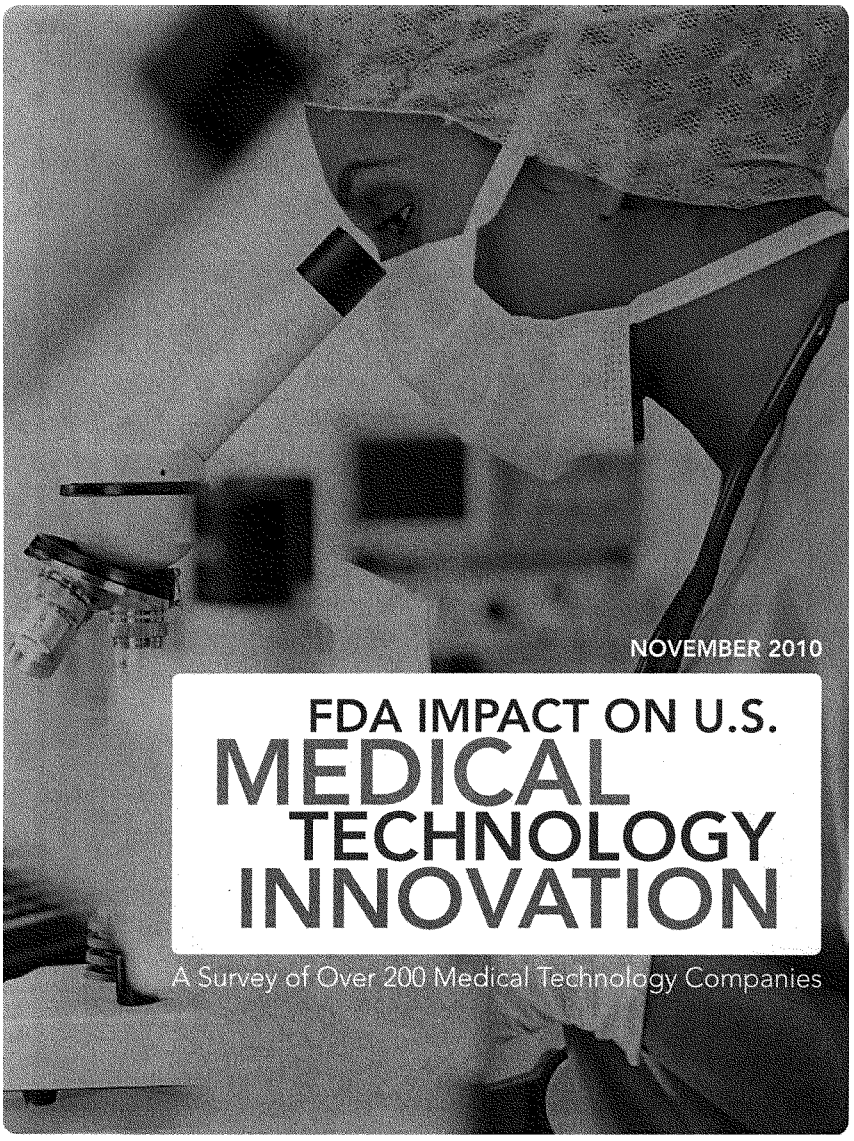
The data presented in this report present a troubling picture of the state of medical device regulation (and its effect on innovation and the advancement of public health) under current FDA policies and practices. The survey results also indicate that the pendulum may have swung too far in one direction and balance again needs to be restored.

As noted, the changes at the FDA that have transpired over the last several years (and that have accelerated in the last two years) have largely been driven by perceived safety concerns. Yet, other than isolated examples and anecdotes, no collective data has been presented to suggest the need for such significant and sweeping adjustments. During this period, regulatory processes in Europe have remained relatively constant, making them a valuable comparator for our own regulatory performance in the U.S. It is clear from the data that the European regulatory process is more predictable, reasonable, and transparent. This system also allows companies to make safe and effective new medical products available to patients more quickly, and at a lower cost. If the same devices become available in U.S. following their European approval only after extensive delays and additional costs are accrued, we must evaluate whether the U.S. premarket regulatory process is truly contributing to the advancement and promotion of the public health, or if it is actually restraining it.

Today, as we face substantial concerns regarding the cost of healthcare, we also must acknowledge that a substantial number of important patient needs still remain unaddressed. A solution to both of these problems cannot be achieved by delaying new innovations and cost-

[11] See "State Impacts of the Medical Technology Industry," op. cit., p. 12.

effective treatments. To truly promote the public health, the FDA must impose reasonable regulatory requirements on new innovations, implement more balanced requirements for premarket and postmarket clinical data, and go back to leveraging market forces to reward technology that presents the greatest value to patients. Only then will the most cost effective advances in medical care be delivered; and only then will the public health and our economy be best served.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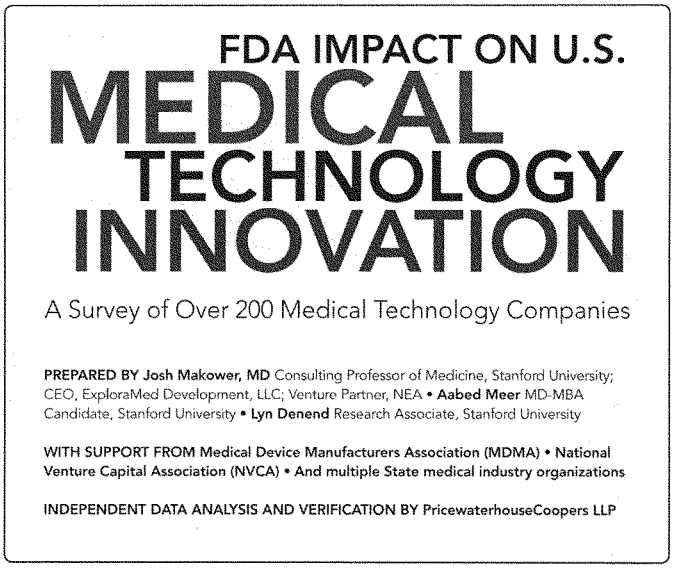
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PREPARED BY Josh Makower, MD Consulting Professor of Medicine, Stanford University; CEO, ExploraMed Development, LLC; Venture Partner, NEA • Aabed Meer MD-MBA Candidate, Stanford University • Lyn Denend Research Associate, Stanford University
WITH SUPPORT FROM Medical Device Manufacturers Association (MDMA) • National Venture Capital Association (NVCA) • And multiple State medical industry organizations
INDEPENDENT DATA ANALYSIS AND VERIFICATION BY PricewaterhouseCoopers LLP

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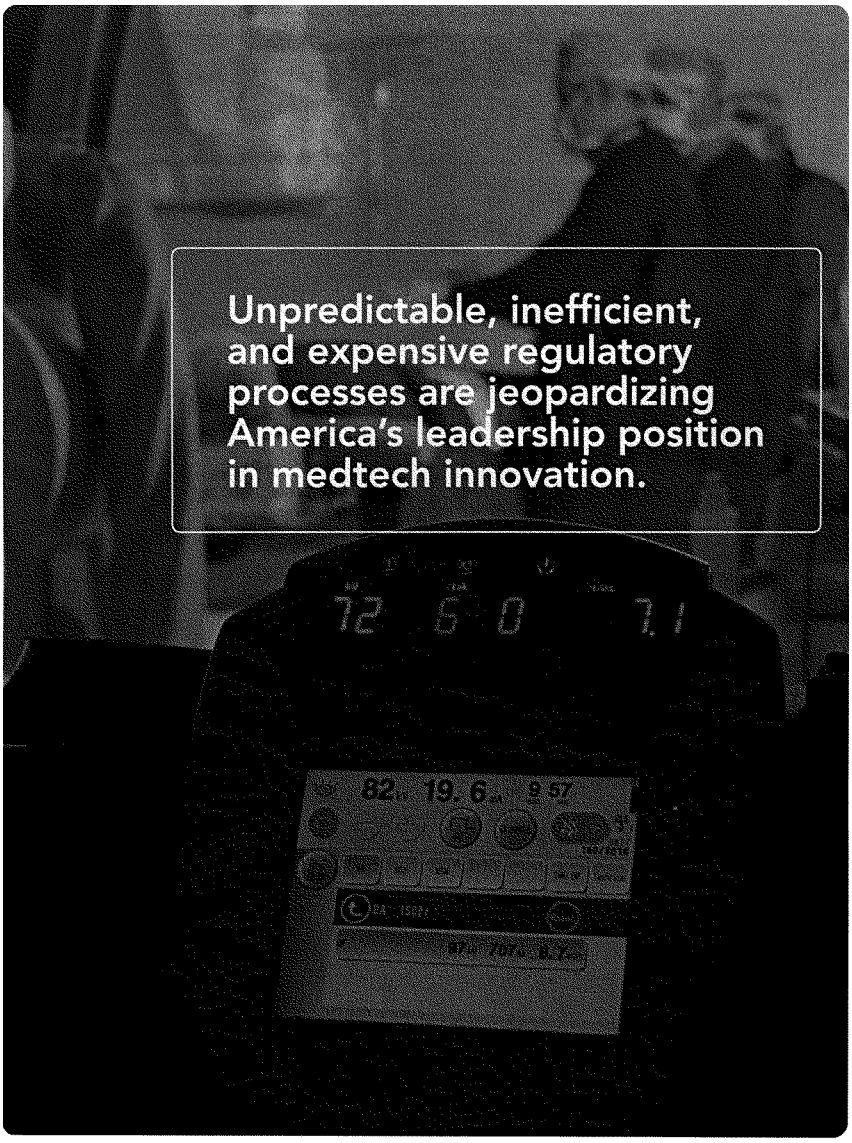

Unpredictable, inefficient, and expensive regulatory processes are jeopardizing America's leadership position in medtech innovation.

EXECUTIVE SUMMARY

Over the past few years, the manner in which the U.S. Food and Drug Administration (FDA) is executing its authority over the regulation of medical devices in the U.S. has been called into question. While some have claimed that current regulatory requirements are lax and harming patients, independent analysis has demonstrated that the current system does an exceptional job of protecting patients.[1] However, with regard to the agency's objective of promoting the public health through new innovations, there are increasing concerns from patients, physicians, and innovators that the FDA is falling short. Until now, little (if any) data has been produced to either validate or refute these concerns.

OVERVIEW

The purpose of this study was to address the need for data that could be used to evaluate the impact of U.S. medical device regulation on innovation and patients. The authors initiated the study in summer 2010 so that the results could be used to inform discussions underway within the FDA and the Institute of Medicine (IOM).

The U.S. regulatory system uses a combination of processes before a product is available to patients (referred to as the premarket period) and after a product has been cleared/approved for market (referred to as the postmarket period) to ensure patient safety and product effectiveness. The study, which took the form of a survey, focused exclusively on assessing premarket regulatory processes. It was used to help determine if concerns about the efficiency of current U.S. regulatory processes were isolated or widespread across the medical technology ("medtech") industry. It was also designed to identify where the greatest deterrents to innovation exist within U.S. premarket regulatory processes and the costs (in time and dollars) these issues place on U.S. medtech companies. This report summarizes the results of the study and explores the implications of the data on patients, innovators, the U.S. medtech industry, and the economy at large.

[1] Ralph Hall, "Using Recall Data to Assess the 510(k) Process," Public Health Effectiveness of the FDA 510(k) Clearance Process: Workshop #2, Institute of Medicine, Washington, D.C., July 2010.

Responses from 204 unique companies are reflected in the study data. This number represents approximately 20 percent of all public and venture-backed medical device manufacturers in the U.S. that are focused on bringing innovative new technologies to market to improve the public health (e.g., devices used to treat hypertension, obesity). Survey participants were asked about their experiences in working with the FDA, as well as their experiences working with European regulatory authorities so that comparisons could be made between aspects of the two dominant regulatory systems that assure the safety of innovative technology in the global marketplace.

RESULTS

In general, survey respondents viewed current U.S. regulatory processes for making products available to patients (the premarket process) as unpredictable and characterized by disruptions and delays. For example, 44 percent of participants indicated that part-way through the premarket regulatory process they experienced untimely changes in key personnel, including the lead reviewer and/or branch chief responsible for the product's evaluation. A total of 34 percent of respondents also reported that appropriate FDA staff and/or physician advisors to the FDA were not present at key meetings between the FDA and the company. Factors such as these make the U.S. premarket regulatory process inefficient and resource intensive.

The above factors also contribute to significant delays in navigating FDA regulatory processes. Survey respondents reported that the premarket process for 510(k) pathway devices (of low- to moderate-risk) took an average of 10 months from first filing to clearance. For those who spoke with the FDA about conducting a clinical study for their low- to moderate- risk device before making a regulatory submission, the premarket process took an average of 31 months from first communication to being cleared to market the device. In contrast, respondents said it took them an average of 7 months in Europe from first communication to being able to market the same (or equivalent) device.

For higher risk devices seeking premarket approvals (on the PMA pathway), responding companies indicated that it took an average of 54 months to work with the FDA from first communication to being approved to market the device. In Europe, it took an average of 11 months from first communication to approval.

The FDA compared unfavorably to European regulatory authorities in other ways, as well:

- **PREDICTABILITY** 85 percent of respondents considered EU authorities to be highly or mostly predictable, while only 22 percent gave the FDA the same ratings.
- **REASONABLENESS** 91 percent of respondents rated EU authorities as highly or mostly reasonable compared to just 25 percent for the FDA.
- **TRANSPARENCY** 85 percent found the processes and decisions of the EU authorities to be highly or mostly transparent compared to 27 percent for the FDA.
- **OVERALL EXPERIENCE** 75 percent of respondents rated their regulatory experience in the EU excellent or very good. Only 16 percent gave the same ratings to the FDA.

The survey data also showed that the average total cost for participants to bring a low- to moderate-risk 510(k) product from concept to clearance was approximately $31 million, with $24 million spent on FDA dependent and/or related activities. For a higher-risk PMA product, the average total cost from concept to approval was approximately $94 million, with $75 million spent on stages linked to the FDA. (These estimates do not include the cost of obtaining reimbursement or any sales/marketing-related activities.) Survey respondents confirmed that they are able to make their products available to patients faster and at a significantly lower cost in markets such as Europe. For U.S. companies, these mounting costs are unsustainable in a venture-backed industry where less than one out of four medtech start-ups succeed, 50 percent of all reported exits[2] are less than $100 million, and the total pool of available investment capital is shrinking.

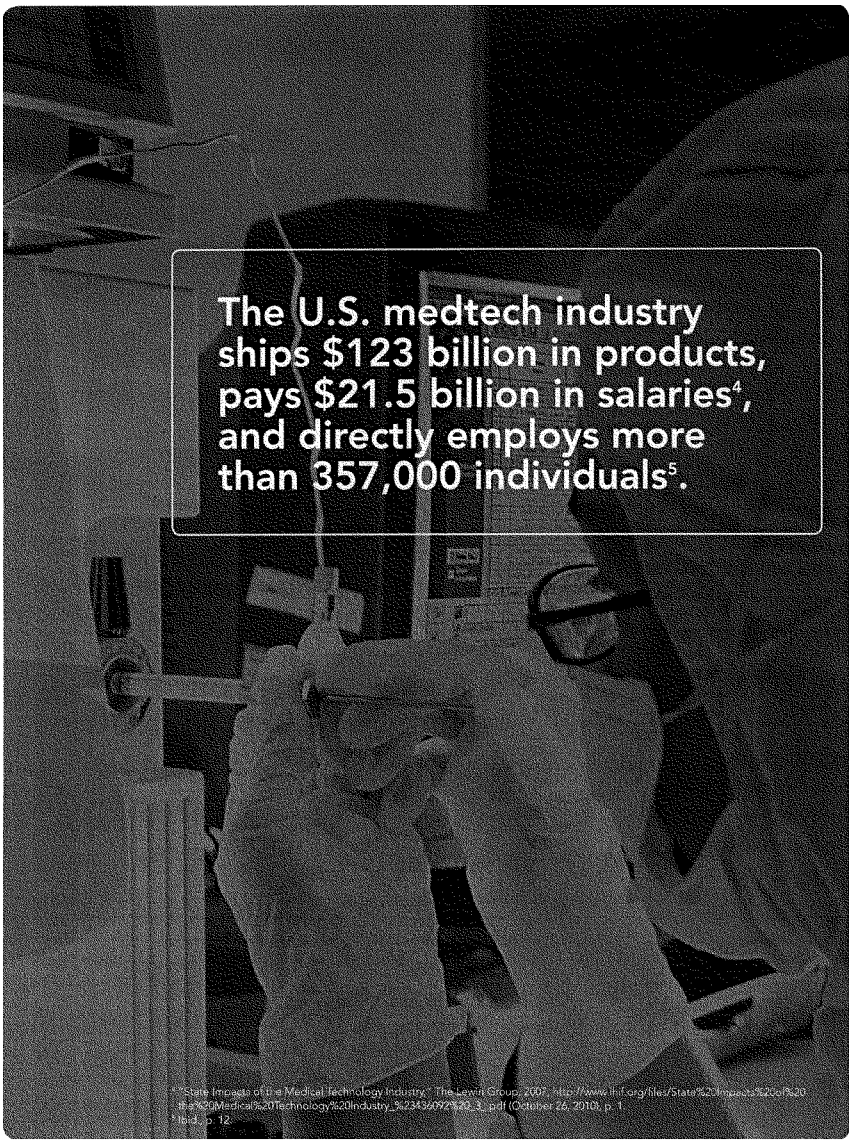
Perhaps most importantly, the survey revealed that the suboptimal execution of FDA premarket regulatory processes has a significant, measureable cost to U.S. patients in the form of a device lag. Respondents reported that their devices were available to U.S. citizens an average of two full years later than patients in other countries, due to delays with the FDA and/or company decisions to pursue markets outside the U.S. before initiating time-consuming, expensive regulatory processes in their own country.[3] In some cases, this device lag reached up to 70 months (nearly six years).

[2] The term "exit" refers to a liquidity event (usually an acquisition or initial public offering) that potentially allows investors to realize a return on their invested capital.
[3] In this context, availability refers to having achieved regulatory clearance/approval to legally market the device; it does include commercialization activities, such as reimbursement or distribution.

IMPLICATIONS

Unpredictable, inefficient, and expensive regulatory processes put the U.S. at risk of losing its global leadership position in medtech innovation. Data from the survey clearly indicate that European regulatory processes allow innovators to make new medical technologies available to patients more quickly and at a lower cost. The reasonable question has been raised whether greater regulatory efficiency in the EU has been achieved at the expense of patient safety. However, no information is currently available to suggest that patient safety in Europe has been compromised. If the same devices become available in U.S. following their European approval only after extensive delays and additional costs are accrued, we must evaluate whether U.S. premarket regulatory processes are truly contributing to the advancement and promotion of the public health, or if they are actually restraining it.

Under current FDA processes, millions of U.S. patients are being denied or delayed access to leading medical devices that are first (or exclusively) brought to market in other countries. Fewer medical device start-ups are being launched in the U.S. as investment capital in the industry continues to move to other sectors. And, innovators and medical device companies are relocating to other countries in greater numbers, taking valuable jobs and tax revenue with them. Regulators and innovators must work together to reverse these troubling trends. To truly promote the public health, the FDA must impose reasonable regulatory requirements on new innovations, implement more balanced requirements for premarket and postmarket clinical data, and go back to leveraging market forces to reward technology that presents the greatest value to patients. Only then will the most effective advances in medical care be developed and provided promptly to American patients; and only then will the public health and our economy be best served.



[4] "State Impacts of the Medical Technology Industry," The Lewin Group, 2007, http://www.ihf.org/files/State%20Impacts%20of%20the%20Medical%20Technology%20Industry_%2343609%20_3_.pdf (October 26, 2010), p. 1.
[5] Ibid., p. 12.

BACKGROUND

In 1976, when the U.S. Congress passed the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, it established a new organization with the FDA that is known today as the Center for Devices and Radiological Health (CDRH). The Center has a two-fold mission to both protect and promote the public health when it comes to the use of medical technologies. However, over the last two years, representatives from the medtech industry have reported that the FDA is becoming less predictable, transparent, and reasonable while, at the same time, its requirements for demonstrating the safety and effectiveness of new devices continue to increase. To better understand if CDRH's current approach toward device regulation effectively balances the two imperatives reflected in its mission, or if the Center has become so cautious that its policies are denying patients timely access to the latest technologies and negatively affecting innovation in the industry, a systematic evaluation of the regulatory oversight process was needed. These factors motivated the initiation of the study described in this report.

THE INDUSTRY

The medtech industry plays an important role in the lives of patients around the world. In this context, medtech refers to medical devices intended for use for therapeutic and diagnostic purposes. Together with other segments of the larger health care sector, medtech companies have contributed to dramatic improvements in health. For example, from 1980 to 2000, new diagnostic and treatment paradigms helped drive an increase in U.S. life expectancy of more than three years, a 16 percent decrease in annual mortality rates, and a 25 percent decline in disability rates for the elderly.[6] During this period, mortality from heart attacks was nearly cut in half. Mortality also declined by more than 30 percent for stroke patients and by over 20 percent for those with breast cancer.[7]

[6] "The Value of Investment in Healthcare," MEDTAP International, 2004, www.aha.org/aha/content/2004/PowerPoint/ValuePresentation.ppt (October 2, 2010).
[7] Ibid.

The U.S. medtech industry also has an essential role in the U.S. economy. In 2006, companies in the field shipped products valued at $123 billion and paid $21.5 billion in salaries.[8] The industry directly employed more than 357,000 individuals and indirectly accounted for another 1.6 million jobs (each direct medtech position generates 4.47 additional jobs in the national economy).[9] Employees in the medtech field earn above average wages—approximately $60,000 per year—because the industry requires and attracts a highly skilled and educated workforce.[10] New medical technologies also have the potential to drive down costs in a world of escalating healthcare expenditures.

Internationally, the U.S. is the largest global consumer of medical devices. However, it is also the world's leading producer. The country achieved this leadership position through decades of strong, sustained investments in research and development (R&D) by U.S. medical device companies and the venture capital community that backs them. As a result, the medtech field is among a limited number of industries in which the U.S. maintains a trade surplus. In 2007, the total medtech trade surplus was estimated at $5.4 billion.[11]

Traditionally, innovation in the medtech industry has been driven by small, entrepreneurial companies with a passion for discovering safer, more effective ways to diagnose and treat patients. Although a number of major device manufacturers exist, more than 80 percent of medtech companies have fewer than 50 employees.[12] These small starts-ups are the engine that fuels the development of innovative new devices, which are often acquired by the larger companies as they mature. Through the combined efforts of both small and large medtech companies alike, R&D investment in the industry more than doubled during the 1990s, and it continues to outpace the R&D investment of companies in other U.S. manufacturing industries by an average of twice as much.[13]

THE FDA

Within the FDA, CDRH has two primary regulatory pathways that medical devices can take to get to market. The Center uses the premarket approval (PMA) pathway to evaluate and approve technologies that are truly novel and pose a high potential risk to the patients using them. For low to medium risk devices, it employs the premarket notification or 510(k) process. Regardless of whether a device must follow the 510(k) or PMA pathway, the FDA has the ability to request that a company provide clinical data to support clearance or approval. This data often requires an allowance by the FDA to perform clinical trials in the U.S., which is known as an investigational device exemption (IDE).

[8] "State Impacts of the Medical Technology Industry," The Lewin Group, 2007, http://www.ihif.org/files/State%20Impacts%20of%20the%20Medical%20Technology%20Industry_%2436092%20_3_.pdf (October 26, 2010), p. 1.
[9] Ibid., p. 12.
[10] Ibid., p. 4.
[11] "Medical Technology and Venture Capital: A Fruitful Yet Fragile Ecosystem," MDMA and NVCA, June 2009, http://www.medicaldevices.org/node/656 (October 2, 2010).
[12] Ibid.
[13] "Medical Devices Industry Assessment," International Trade Administration, 2009, http://www.ita.doc.gov/td/health/Medical%20Device%20Industry%20Assessment%20FINAL%20II%203-24-10.pdf (October 2, 2010).

Early in the implementation of section 510(k) of the Medical Device Amendments, it was well recognized that the 510(k) pathway to market could efficiently facilitate the availability of new technologies that have the same intended use as legally marketed devices without creating an undue regulatory burden. This approach was meant to allow companies to build upon established clinical and scientific evidence of safety and effectiveness to more rapidly iterate and improve the innovations available to patients. Not surprisingly, the 510(k) process is more widely used than the PMA pathway. In 2009, for example, CDRH approved just 15 original PMA submissions while it cleared approximately 3,000 products under a 510(k).[14]

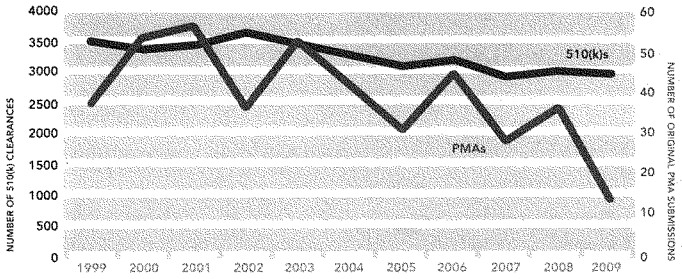
As it shepherds technologies through these two pathways, the FDA must balance the imperative of assuring the safety, effectiveness, and quality of commercially available medical devices with its mission of fostering innovation by providing companies with a timely, predictable route to market. In recent years, some politicians, members of the press, and consumer groups have criticized the FDA for not adequately addressing the safety of medical devices, particularly those cleared through the 510(k) pathway. Driven by anecdotal examples reported in the media, these concerns have persisted despite compelling evidence that both the 510(k) and PMA pathways are fulfilling their intended purpose in protecting patients. For example, one recent study demonstrated that 99.6 percent of all 510(k) and PMA devices cleared/approved by the FDA between 2004 and 2009 have never had a Class I[15] recall.[16] (Recalls are an indicator of major device problems that have the potential to negatively affect patient safety and/or device effectiveness.) Such results demonstrate that serious device-related safety problems are extremely rare. Also, the data show that the majority of these rare postmarket events stem from issues relating to quality systems and manufacturing processes and not issues that would have been most effectively detected through more expansive premarket data requirements.

[14] Calculated from FDA data available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm and http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm (October 22, 2010).
[15] A Class I recall is the most serious type of FDA recall because the problem for which the device has been recalled may result in major injuries or death.
[16] Hall, op. cit.

Despite this evidence, the FDA's clinical data requirements continue to rise. While the agency historically used the postmarket period to continue accruing data regarding device safety and effectiveness (allowing the market to determine the value of a medical device), it is increasingly demanding that this kind of large-scale clinical data be provided during the premarket period. When it comes to premarket data requests for new products, medtech innovators say they face more uncertainty regarding the FDA's expectations, and that bench, animal, and clinical testing requirements are mounting without clear justification or benefit. Even more troubling are an increasing number of examples from industry representatives that FDA reviewers are requesting esoteric scientific testing, or posing questions that are not reasonably answerable, sometimes at great expense and with little relevance to safety and effectiveness. Moreover, medtech innovators have reported that the FDA is becoming less predictable and increasingly inefficient in its premarket review role. Stakeholders maintain that the CDRH, over the last several years, has become even less transparent in how it makes decisions, as well as slower in responding to inquiries and regulatory submissions. The degree to which these reports represent isolated incidents versus a general trend was unknown prior to the completion of this study.

According to device companies, these changes have created nearly insurmountable barriers to medtech innovation in the U.S., with no apparent off-setting public health benefit. The current regulatory environment is particularly challenging for start-up companies, which have historically played a key role in driving innovation, because of their limited financial resources. As a result, regulatory submissions for innovative new medical devices have been declining in the U.S. over the last several years. Clearances/approvals are also trending downward (as shown in Figure 1). In an era of greater scientific knowledge and technology advancements than any other time in history, one must question what forces are driving medical technology innovation in a negative direction.

FIGURE 1 – 510(k) CLEARANCES AND PMA APPROVALS (1999-2009)



SOURCE: Calculated from FDA PMA approval and 510(k) clearance data.[12]

In 2009, CDRH launched two working groups to evaluate: (1) the 510(k) program, and (2) how the Center uses scientific data to support its regulatory decision making. Similarly, the IOM convened a committee at the FDA's request to assess the effectiveness of the 510(k) process. As these groups gather information, formulate recommendations, and solicit public comment, objective data must be considered that bears on the role of the FDA in protecting the public health and the adequacy of the agency's regulatory processes (as noted above). Until now, there has been little systematic information to validate or disprove the anecdotal reports of the deleterious effects that FDA regulation has on U.S. patient access to new medical technology, device innovation in the country, and America's medtech leadership position in the world.

The purpose of this study was to gather quantitative and qualitative data from a representative subset of medtech companies to elucidate the impact of the FDA's current regulatory practices on medical technology innovation and the advancement of public health so that Congress, the FDA, and the IOM would have more information to consider in their evaluations.

[12] Calculated from FDA data available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm and http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm (October 22, 2010). It was not possible to calculate the percentage change in clearances/approvals from year to year because data regarding the total number of 510(k) and PMA submissions is not made publicly available by the FDA.

STUDY METHODOLOGY

To obtain a more systematic understanding of the perceptions and experiences of medtech companies in dealing with the FDA, the study authors designed a survey. This survey was created to collect information from medtech industry executives about the how U.S. and European premarket regulatory processes compare, the cost and time to navigate the U.S. premarket regulatory processes, and what aspects of the U.S. premarket regulatory processes are most challenging to innovators.

Input on the questions was requested from MDMA, NVCA, and a variety of relevant state associations including the California Healthcare Institute (CHI), MichBIO, MassBIO, PA BIO, Life Science Alley (Minnesota), MedTech (NY), Colorado Bioscience Association, Florida Medical Manufacturers' Consortium, and Washington Bio. Feedback was also solicited from the FDA, with several CDRH leaders providing input.

Once the questionnaire was developed, participants were recruited through two primary channels. MDMA sent the survey to its 260 members. NVCA also distributed the questionnaire to 211 of its members—venture capital firms with a presence in the life sciences field. These firms were then asked to pass it along to the medtech companies in their investment portfolios. If all of the medtech portfolio companies had been sent the survey, it would have reached approximately 750 potential participants.

Medtech companies were given two options for participating in the survey: they could respond to the questions via an in-person or telephone-based interview; or they could provide their answers electronically by entering them into a web-based form. The online form included a slightly smaller subset of the most relevant survey questions, so it was quicker to complete.

During the data collection period, 100 phone interviews were conducted, primarily with MDMA members. In total, 95 MDMA members expressed interest in taking the survey, but only 80 could be scheduled for a phone interview (for a 31 percent MDMA participation rate). Another 20 companies heard about the survey through other mechanisms (e.g., the state associations listed above) and also participated via phone.

Participants reached through NVCA responded via the online survey. In total, 176 companies completed the web-based questionnaire, but only 131 provided trackable data (meaning, it allowed independent verification of their identities and qualifying answers). Out of a possible 750 portfolio companies, this resulted in a 17 percent NVCA response rate.

Duplicate entries from MDMA and NVCA members were eliminated, leaving responses that represented experiences for 213 unique products from 204 companies. A small number of companies were permitted more than one response if their regulatory experiences varied significantly for two different products, or if more than one department responded within a larger medtech organization. However, the vast majority of the companies in the survey were small, early-stage entities, focused on a single product family.

In terms of characterizing the respondents, 90 percent were private companies; 10 percent were publicly-held. The majority were venture-backed and considered to be small in size (median = 33 employees). When interacting with the FDA, 55 percent had completed a traditional 510(k) for a low- to moderate-risk device; 32 percent went through the PMA process for a higher-risk device; and 13 percent navigated other regulatory pathways (special 510(k)s, de novo 510(k)s, or for humanitarian use devices). A comparison of the survey participants to U.S. medtech industry data published in Ernst & Young's 2010 "Pulse of the Industry: Medical Technology Report," is shown in Table 1.

TABLE 1 – COMPARISON OF INDUSTRY VERSUS PARTICIPANT DEMOGRAPHICS

U.S. INDUSTRY	PARTICIPANTS
1,023 public and venture-backed medtech companies	204 public and venture-backed medtech companies
>50 percent of companies in California, Minnesota, and Massachusetts	>50 percent of companies in California, Minnesota, and Massachusetts
Largest specialties within the market are cardiovascular, orthopedics, and non disease-specific	Largest clusters of participants are from orthopedics, cardiovascular, and general and plastic surgery

SOURCE: U.S. industry data drawn from Ernst & Young's *"Pulse of the Industry: Medical Technology Report,"* 2010.

While there are more than 16,000 "medical device companies" registered with the FDA, this figure includes thousands of organizations that supply components to device manufacturers, sterilization service companies, contract laboratories, and other non-product producing enterprises. Of the total, 4,776 are categorized as medical device manufacturers, yet an unknown number are defunct or never produced products. Larger companies in this grouping may also have multiple registrations per entity. In addition, over the past few years, only a minority of these companies filed premarket submissions with the FDA. Thus, this larger FDA-registered group does not represent a reasonable denominator to assess the study subset.

In contrast, the medtech companies included in the Ernst & Young profile are product-driven medical device manufacturers actively working on bringing innovative new medical technologies to market (i.e., those smaller companies that represent the medtech innovation engine). This subset more closely mirrors the population the study was designed to reach. If one considers these 1,023 medtech companies as the target population for the survey, approximately 20 percent of U.S. medtech industry innovators responded to the survey (204 unique companies).

After the study was conducted, the survey, survey database, and study analyses were submitted to PricewaterhouseCoopers LLP to ensure their integrity and verify the way in which the study's results were calculated. PricewaterhouseCoopers did not assess the study methodology, but focused solely on assuring that the data collection was accurate and that the results were calculated and presented properly. The data summarized in this report reflects these verified study results.

All of the medtech companies that participated in the study were assured that their responses would be kept confidential. For this reason, we can only present study results in an aggregated format so that company-specific information is not revealed. Examples included in this report reflect the actual experiences of specific medtech companies without details that would compromise the confidentiality of individual participants.

STUDY LIMITATIONS

While the data from more than 200 companies provide a compelling look at current U.S. regulatory practices and their effect on innovation in the medical device industry, there are some potential limitations to the study.

First, there may be selection biases within the sample. MDMA, NVCA, and state association members were the only companies formally invited to participate in the study. Public and venture-backed medtech companies are more likely to develop novel technologies that may be most impacted by the current FDA environment.

Additionally, participation was voluntary. This could mean that companies with issues to report may be more likely than others to respond to the survey; however, we also know that some companies with complaints were unwilling to participate. A number of companies indicated that they would not respond due to fear of retribution from the FDA (despite assurances we would maintain their confidentiality). Others said they were too busy. The remaining companies had other reasons for not participating that are unknown to the authors.

Beyond this, other sources of potential bias may exist. Specifically, some of the study authors have either direct or indirect industry affiliations. Moreover, survey participants themselves may be subject to certain biases based on their personal experiences with the FDA and their business interests within the industry being studied.

Lastly, the representative "n" for each question varies across the survey for several reasons:

- Some questions were designed to apply only to certain subsets of the survey respondents (e.g., specific questions were asked only of those companies that had pursued a 510(k), or required an IDE, or sought a CE mark, etc.).
- Survey responses collected via the 100 telephone interviews used a more expansive, detailed questionnaire, whereas the "online" survey was shorter and more focused.
- In some cases, respondents could not reply to all questions due to a lack of information. In other cases (particularly with the online survey), they may not have completed all fields and no explanation was provided. When this occurred, missing responses were excluded from the sample for those questions.

Despite these potential limitations, this study is among the first to attempt to provide a representative view of the medtech industry's experiences in the current FDA environment. It significantly advances the available data that can be used to help assess regulatory impact on innovation in the U.S. medical device industry and the ability of U.S. companies to make progress toward affording American citizens access to the best technology under today's regulatory conditions. It is also the first coordinated effort by MDMA, NVCA, and a majority of the medtech state associations.

STUDY RESULTS

Results from the survey are summarized below in four primary sections: (1) efficiency of U.S. regulatory processes and how they compare to the EU, (2) perceptions of FDA performance relative to European regulatory authorities, (3) cost to medtech companies, and (4) cost to U.S. patients.

EFFICIENCY OF U.S. REGULATORY PROCESSES AND HOW THEY COMPARE TO THE EU

The FDA and European regulatory authorities both have a solid track record of ensuring the overall safety and effectiveness of the devices that are made available within their jurisdictions. However, survey respondents reported that the FDA's current practices are less efficient than the agency's European counterparts. The general efficiency of regulatory processes can be measured by the time it takes to accomplish key milestones, as well as the presence (or lack) of process disruptions.

In terms of process disruptions, the survey explored problems that could contribute inefficiencies and delays. For example, 44 percent of participants indicated that part-way through the regulatory process they experienced untimely changes in key personnel, including the lead reviewer and/or branch chief responsible for the product's evaluation. In these cases, companies experienced a significant setback having to retread ground that had already been covered. In addition to the delays caused by a lack of continuity in a review team, new reviewers may have different expectations, which can lead to inconsistencies, frustration, and additional resource demands.

A total of 34 percent of respondents also reported that appropriate FDA staff and/or physician advisors to the FDA were not present at key meetings. For instance, representatives from several companies reported that non-practicing physicians were brought in to work as consultants to augment the FDA reviewers evaluating their devices. The concern in these cases was that the physicians were not familiar with current treatment paradigms and the companies had to spend time discussing recent advancements in the field. Different challenges arose when physicians without the appropriate background or training were assigned work on a review team (e.g., an ophthalmologist called in to assess a cardiovascular device).

From a timing perspective, the CDRH's Office of Device Evaluation (ODE) reported in its FY2009 fiscal year performance report that the "average FDA review time" for a 510(k) was just over two months (63 days). The "average total elapsed time from receipt to final decision" was more than 3 months (98 days).[18] However, these FDA-reported averages likely underestimate the actual time required achieve 510(k) clearance for several reasons. First, the FY2009 cohort is still incomplete due to an unknown number of decisions on 2009 submissions that are still pending within the agency. Second, the FDA has no established way of tracking the true timing of the process for an individual company or product as it navigates the regulatory/clinical process; the agency simply reports on the average time a file is open in its offices for a particular type of request (IDE, 510(k), PMA, etc.). This practice can potentially be misleading. With FDA limiting the number of attempts that companies have to demonstrate substantial equivalence in the confines of a single 510(k), requesting 510(k)s be voluntarily withdrawn, and deleting 510(k)s based on the passage of time, average review times have limited value. Fundamentally, the more relevant metric for patients and the industry is how long it takes for a new product to navigate the entire regulatory process until it is cleared or approved for market. The survey tried to quantify this data and how timing in the U.S. compares to timing in Europe.

When measuring comparative review times for the FDA and European regulatory authorities among survey respondents, two starting points were considered. If the filing of a formal submission for clearance or approval was the initiating event for the first interaction between a company and a regulatory body, the date of "first filing" was used as the index date. For most simple, low-risk products (e.g., 510(k)s), companies commonly make a regulatory submission prior to interacting with the regulatory body. However, in a majority of cases, companies either communicate with the regulatory bodies and/or file other documents with the regulatory body (e.g., requesting a pre-IDE meeting to discuss the design of a possible clinical trial, or filing an IDE). In such cases, the date of "first communication" was used as the index. In all cases, products likely to require clinical trials initiated their regulatory process with a communication either alone or in combination with a formal filing. Either way, the earliest interaction between company and regulatory body was used as the starting point for evaluating U.S. and European review timelines relative to one another.

[18] "Annual Performance Report," Office of Device Evaluation, Fiscal Year 2009, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM223893.pdf (October 4, 2010), pp.8-9.

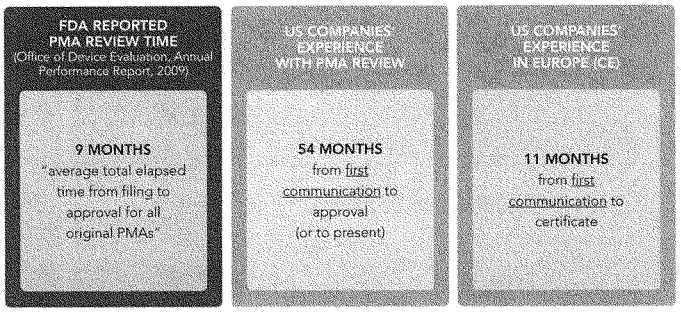
According to the survey, U.S. companies that navigated the 510(k) pathway stated that it took them an average of 10 months from first filing to clearance.[19] Responses from those who had communicated with the FDA prior to making a 510(k) submission indicated that the total elapsed time from first communication to clearance (including any pre-IDE[20] or IDE related interactions) was an average of 31 months. (Note that a relatively small subset of respondents (n = 15) is reflected in this data point because most companies do not have contact with the FDA prior to making a 510(k) submission.) In contrast, survey participants found their interactions with regulatory officials in Europe to be much more timely. On average, they said it took 7 months from first communication to the time that CE mark certification was awarded.[21] A comparison of U.S. and EU timelines is shown in Figure 2.

FIGURE 2 – 510(k) AND CE MARK REGULATORY TIMELINES

Survey respondents reported similar experiences with the PMA pathway. In its fiscal year 2009 annual performance report, the ODE stated that its "average total elapsed time from filing to approval for all original PMAs" was just over 9 months (284 days).[22] However, survey participants indicated that it actually took them an average of 54 months to work with the FDA from first communication to approval (or until the time of the survey, if the review was still in progress). In Europe, an equivalent product review took an average of 11 months from first communication to CE mark certification (as shown in Figure 3).

[19] First filing refers to the point at which a formal submission is made to the FDA.
[20] The "pre-IDE" program includes pre-submission meetings used to discuss premarket requirements that are not related to clinical studies and IDE requirements.
[21] In the European Union, a CE mark is awarded to indicate regulatory approval.
[22] "Annual performance Report," op. cit., p. 5

FIGURE 3 – PMA AND CE MARK REGULATORY TIMELINES



For products requiring an IDE, the ODE reported that the "average review time" was 27 days in fiscal year 2009 and that 99 percent of all original IDE decisions were issued in 30 days.[23] However, according to participants in the survey, the average time required to obtain an IDE was nearly 14 months. The FDA's data indicates that just 56 percent of IDE submissions are approved in the first review cycle. In the remaining 44 percent of cases, the agency requests additional information from the submitting companies, necessitating extended review times.[24] The FDA may also count "conditional approvals" as IDE approvals, even though many studies cannot commence because of the additional conditions that the FDA imposes. Similarly, the FDA may count approvals of feasibility studies as IDE approvals, even if a feasibility study was not proposed. Finally, some IDEs are withdrawn at the FDA's suggestion, or they are converted to pre-IDEs. According to ODE data, the average review time for pre-IDE submissions was 92 days in FY2008 but jumped to 156 days (more than five months) in FY2009.[25]

[23] "Annual performance Report," op. cit., p. 10.
[24] Ibid.
[25] Ibid., p. 12.

Survey respondents said that many delays were linked to clinical trial-related disagreements with the FDA regarding the definition of primary efficacy endpoints (27 percent), the definition of primary safety endpoints (15 percent), and other factors such as the use of historical controls (8 percent), size of the trial (12 percent), statistical techniques (6 percent), and/or the need for randomization (5 percent). Once an IDE was obtained, it took respondents an average of 21 months to conduct a pivotal trial that was designed to satisfy the FDA's requirements with no assurance of the adequacy of the FDA-mandated study design.

PERCEPTIONS OF FDA PERFORMANCE RELATIVE TO EUROPEAN REGULATORY AUTHORITIES

In addition to issues related to the efficiency of the regulatory review process, survey respondents perceived that there were other important differences between the FDA and European regulatory authorities in the area of clinical, engineering, and statistical competence, predictability, reasonableness, and transparency. Overall, the FDA was perceived to be less efficient in performing premarket reviews relative to its European counterparts.

When asked about the knowledge of reviewers, survey participants found 88 percent of EU reviewers to be highly or mostly competent in their *clinical competence* compared to just 47 percent of U.S. reviewers. Similarly, 91 percent of EU reviewers were considered to be highly or mostly proficient in terms of their *engineering competence* compared to 52 percent in the U.S. Additionally, 79 percent of EU reviewers were believed to be highly or mostly *competent in statistics* versus 60 percent in the U.S.

The survey results were similar in the area of *predictability*, with 85 percent of respondents considering EU regulatory authorities to be highly or mostly predictable. By comparison, only 22 percent gave the FDA the same ratings (see Figure 4). The majority of survey participants believed the agency to be somewhat predictable (25 percent), mostly unpredictable (22 percent), or very unpredictable (31 percent).

Respondents also found EU regulatory authorities to be more *reasonable*. A total of 91 percent of respondents rated them as highly or mostly reasonable compared to just 25 percent for the FDA (see Figure 5).

In terms of *transparency*, 85 percent found the processes and decisions of the EU authorities to be highly or mostly transparent compared to 27 percent for the FDA (see Figure 6).

Finally, survey participants rated EU regulatory authorities better *overall*, as shown in Figure 7. A full 75 percent rated their overall regulatory experience in the EU excellent or very good, while only 16 percent gave the same scores to the FDA.

Beyond these direct comparisons, 93 percent of participants in the study agreed or strongly agreed that FDA has become more risk-averse toward new products in the last decade. Specifically, medtech executives and entrepreneurs who started companies and/or took devices through the regulatory process in the late 1990s and early 2000s stated that the agency now seems to be more risk averse and hesitant to make decisions, which could create delays and make the process less predictable and more costly. Additionally, 81 percent of respondents agreed or strongly agreed that the FDA has a particularly difficult time dealing with truly novel technologies (e.g., drug/device combinations and others PMA products). Finally, 66 percent expressed frustration that changes at the FDA had some negative impact or a strong negative impact on the progress of their companies on the way to market.

SURVEY RESPONDENT RATINGS OF FDA AND EU REGULATORY PERFORMANCE

FIGURE 4 – FDA VERSUS EU – PREDICTABILITY FDA (n=120) CE (n=83)

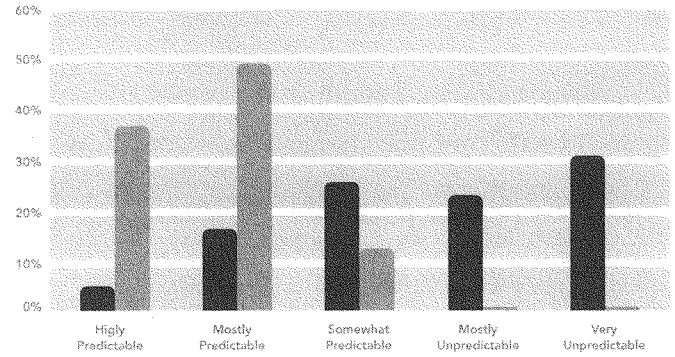


FIGURE 5 – FDA VERSUS EU – REASONABLENESS FDA (n=124) CE (n=86)

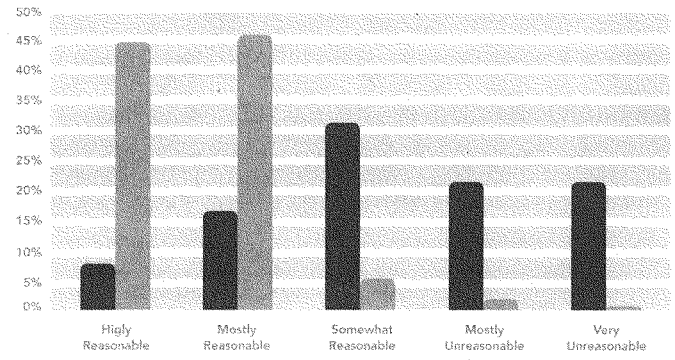


FIGURE 6 – FDA VERSUS EU – TRANSPARENCY FDA (n=119) CE (n=81)

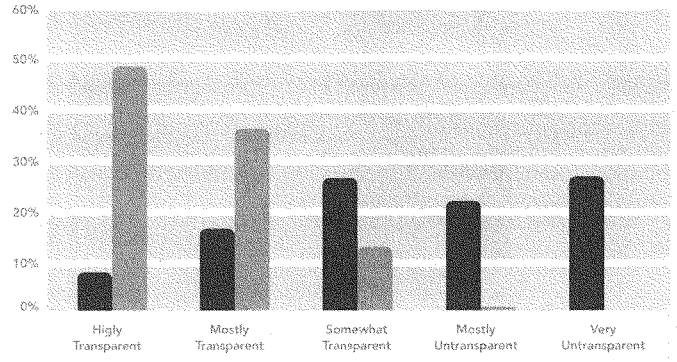
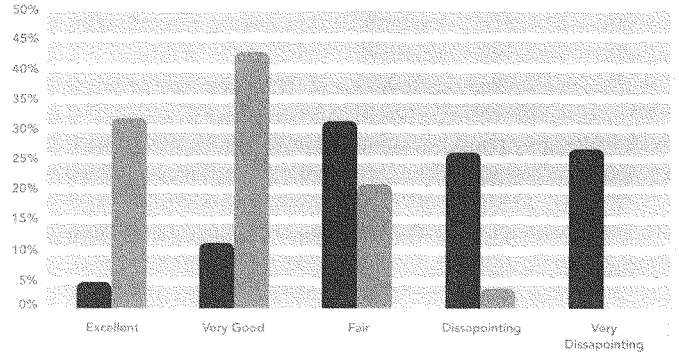


FIGURE 7 - FDA VERSUS EU – OVERALL EXPERIENCE FDA (n=119) CE (n=83)
Company experience with regulatory agency



THE COST TO MEDTECH COMPANIES

Inefficient regulatory processes can be devastating to medtech companies because so many of them are smaller start-ups without the cash flows or reserves to endure costly delays. In the survey, participants were asked calculate the amount of time (in months) they spent on critical stages in the medtech product development cycle for products taking the 510(k) pathway, as shown in Figure 8. Then, they were asked to estimate their average monthly expenditures during each stage, as shown in Figure 9. Data from the survey respondents was then used to calculate the total average expenditure to navigate each medtech development stage, as shown in Figure 10). The same three questions were asked for products on the PMA pathway, as shown in Figures 11 through 13.

When clinical or other data is reasonably required and regulatory processes work efficiently, companies must assume these costs as a hurdle for access to any market. However, if additional costs are incurred due to FDA inefficiencies and/or unreasonable delays, products could become prohibitively more expensive to bring to market in the U.S. For example, according to the survey data, every additional month a company spends attempting to obtain an IDE costs nearly $400,000 per month for a 510(k) product and more than $750,000 for a PMA product. Every additional month working through the 510(k) or PMA process itself costs more than $520,000 and $740,000 per month, respectively. These high expenditure levels may help drive higher prices for medical technologies when they finally reach the market. Thus, FDA-related delays directly contribute to increased health care costs in the United States.

The survey data also revealed that the average total cost for participants to bring a 510(k) product from concept to clearance was approximately $31 million, with $24 million spent on FDA dependent and/or related activities. For a PMA, the average total cost from concept to approval was $94 million, with $75 million spent on stages linked to the FDA. (Note that these estimates do not include the cost of obtaining reimbursement approval or any sales/marketing-related activities.) The magnitude of these figures confirms the likelihood that the companies that self-selected to participate in the survey were most likely those companies working on innovative, new medical technologies that required clinical data to get though the FDA rather than those seeking relatively simple extensions to low-risk, ubiquitous product lines already in existence.

IMPACT OF FDA DELAYS IN TERMS OF TIME AND COST

FIGURE 8 – AVERAGE TIME BY STAGE FOR 510(k) PRODUCT

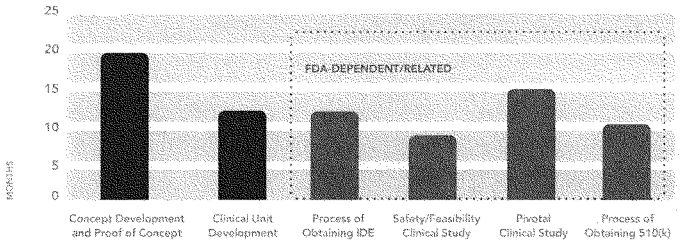


FIGURE 9 – AVERAGE PER MONTH EXPENDITURE BY STAGE FOR 510(k) PRODUCT

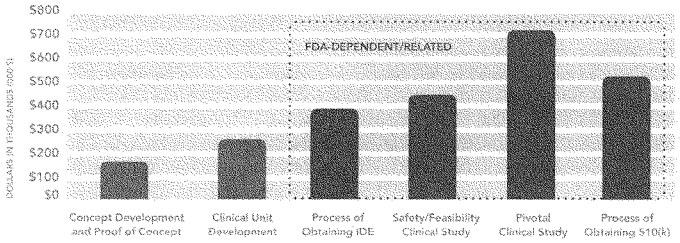


FIGURE 10 – AVERAGE TOTAL EXPENDITURE BY STAGE FOR 510(k) PRODUCT

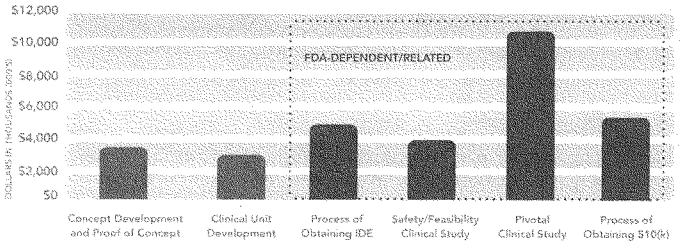


FIGURE 11 – AVERAGE TIME BY STAGE FOR PMA PRODUCT

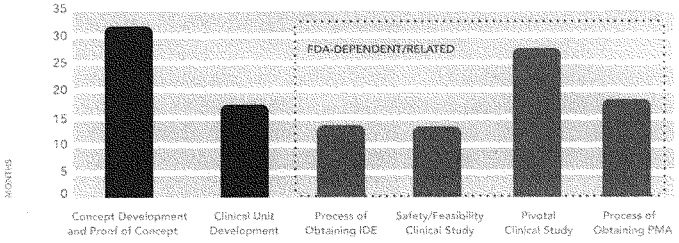


FIGURE 12 – AVERAGE PER MONTH EXPENDITURE BY STAGE FOR PMA PRODUCT

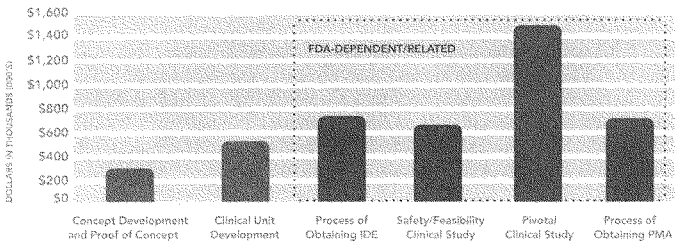
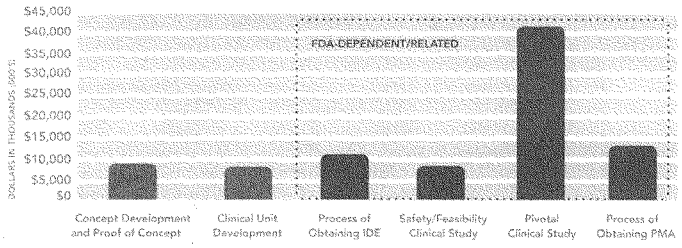


FIGURE 13 – AVERAGE TOTAL EXPENDITURE BY STAGE FOR PMA PRODUCT

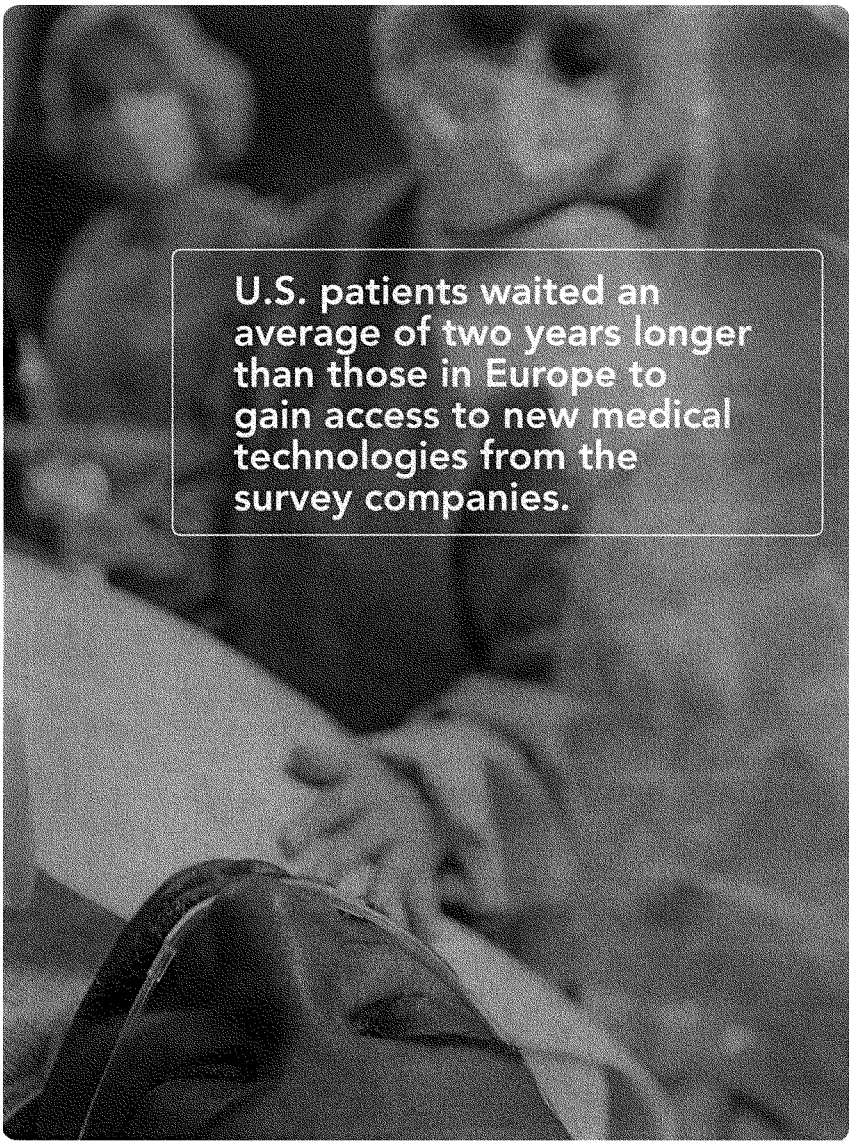


THE COST TO U.S. PATIENTS

Importantly, suboptimal regulatory processes can also have a cost to patients that is much more significant than the additional dollars companies must spend to get their products to market. While U.S. citizens used to be the first to gain access to innovative new technologies, they now face a device lag. Stated another way, U.S. citizens gain access to new U.S.-made medical technologies later than patients in other countries.

On average, the products represented in the survey were available to patients in the U.S. a full two years after they were available to patients in Europe (range = 3 to 70 months later). In some cases, respondents said they initiated their regulatory processes within and outside the U.S. at the same time, but received clearance/approval in the U.S. much later. In anticipation of long, expensive FDA reviews, others said they decided to seek or obtain European approval first in an effort to generate sales overseas that could help fund their U.S. regulatory efforts. Alternatively, some companies reported that they were now setting up operations overseas and developing strategies that do not rely on the U.S. market, despite the fact that it remains the world's largest and most commercially lucrative device market.

Based on the prevalence of the diseases addressed by the companies in the study, this means that millions of Americans do not have access to the latest, most innovative medical technologies. Responding companies reported long delays for U.S. approvals relative to Europe for products offering significant advances for treating or diagnosing highly prevalent conditions such as heart disease, lung disease, obesity, and arthritis. The study data clearly paints a grim picture for patients, as well as medtech innovators relative to the challenges they face as they approach the regulatory stage(s) of their product development process in the United States.


U.S. patients waited an average of two years longer than those in Europe to gain access to new medical technologies from the survey companies.

DISCUSSION

Since the Medical Device Amendments were enacted nearly 35 years ago, medtech regulation has often been described as a pendulum that swings between risk-tolerant and risk-averse regulatory oversight. Over the last two years, the FDA seems to be in the midst of yet another swing toward more risk-averse practices. The forces that drive these oscillations are powerful and deeply rooted in the culture of FDA, as well as in the shifting expectations imposed on the agency by the administration in charge at any particular time. Patients, the public, the media, medtech employees, the scientific community, practicing physicians, and politicians—for better or for worse—all play a role in influencing the FDA's position.

The agency's challenge is clearly to anchor its policies in the position that best serves the public health and is devoid of significant shifts from political influence. The FDA's target is to balance its activities at a some point between the two extremes. However, because some of the stakeholders listed above often have limited or no information about other stakeholders' activities, striking an appropriate balance can be difficult—particularly when prevalent beliefs and behaviors are based on perceptions, headlines, and anecdotes rather than actual data.

This survey attempts to bring forward data that can be used to help inform the discussions currently underway at the FDA and within the IOM regarding the best path forward for medical device regulation. While the challenges we face today are complex and multivariate, and many questions still remain, our hope is that the results of the study will help regulators and innovators work together to achieve a balance that ultimately serves the best interests of patients and the U.S. economy at large.

One of the primary objectives of the survey was to determine if the concerns raised by representatives of the medtech industry regarding the changing environment at the FDA were relatively widespread, or simply the complaints of a vocal minority. The results clearly demonstrate that inefficiencies, delays, and the mounting costs of the U.S. regulatory process are being felt widely across innovators in the industry.

Through the study, we also hoped to shed light on where the greatest problems exist. The data point to troubling inefficiencies caused by reviewer turnover, inconsistent quality and participation of expert advisors, and excessive delays, particularly compared to the FDA's European regulatory counterparts. Participants were asked about their experiences with European regulatory authorities so that comparisons could be made between aspects of the two dominant regulatory systems that assure the safety of innovative technology in the global marketplace.

The study revealed that it takes significantly longer to navigate U.S. regulatory processes than it does to complete European approvals for the same products. Respondents also shared a relatively widespread perception that the FDA has become less reasonable, transparent, and predictable as compared to Europe's regulatory authorities. In combination, these factors had a significant effect on respondents' overall experience with the FDA. More than half of all survey participants said they found their interactions with the agency to be disappointing or very disappointing. These results suggest that the agency is not actively partnering with medtech employees to work toward mutually satisfactory results and the benefit of health care in the U.S.

Finally, the study sought to quantify the costs of regulatory inefficiencies and other delays on patients and companies in the medtech industry. What we learned is that there is a device lag—innovative new medical technologies are becoming available to U.S. patients an average of two years later than patients in Europe (in some cases, the device lag is up to almost six years).[26] The true cost of this lag is difficult to estimate, but one can hypothesize that millions of patients may not be afforded the opportunity to benefit from the best possible care as they await better or different treatments that are commonly being used in other countries. With no available evidence to suggest that the safety of these devices is being substantially improved as they navigate the U.S. regulatory process (relative to Europe), it is reasonable to question whether the lengthy and expensive FDA process is truly protecting patient health, or more simply delaying patient access to new therapies that are available years earlier in other geographies.

The study documented, in time and dollars, what it takes to navigate the core steps in the regulatory process on the way to market in the U.S. Obtaining an IDE, a 510(k), and/or a PMA is both expensive and time consuming. However, the time and cost associated with conducting the types of pivotal clinical trials increasingly required by the FDA is particularly alarming. As data requirements from the FDA have risen, the complexity of the requested studies, as well as the number of patients for which data are required, is proving to be prohibitive to medtech innovators and investors alike.

To help us better understand the implications of the survey data to U.S. patients, innovators, investors, medtech employees, and the economy at large, we shared the findings with a patient (Marti Conger), three innovators (Robert Fischell, Rodney Perkins, and Paul Yock), three medtech investors (Ryan Drant, Ross Jaffe, and Hank Plain), and a medtech industry observer (David Cassak). Their perspectives are reflected in the discussion below.

[26] As noted, availability refers to having achieved regulatory clearance/approval to legally market a device.

IMPLICATIONS TO PATIENTS

As noted, one of the most troubling outcomes of the survey is that U.S. patients are increasingly less likely to be the first to have access to innovative new medical technologies, even when those devices are invented in the U.S. As medtech innovators and employees anticipate time-consuming, expensive FDA regulatory processes, a growing number are taking their devices elsewhere before making them available to American patients. One effect of this trend is that the U.S. is losing its position as the leading provider of medical care. "Our world famous U.S. hospitals are not receiving as many patients from all over the world because the most advanced health care is not being practiced in the United States because of the FDA," stated Dr. Robert Fischell, a serial inventor and founder of multiple medical device companies.

Another effect is that U.S. patients are being forced to pursue leading-edge devices and their associated procedures overseas. As Ryan Drant, a general partner with venture capital firm NEA, put it:

> "Frankly, it's a tragedy. Some of these devices are safely and effectively on the market in Europe for five years before the FDA will even allow them to be used in U.S. clinical trials. The thought that people have to decide whether to forego some potentially lifesaving technology or fly to Europe and figure out some way to pay for it out of pocket, I find very troubling."
>
> — RYAN DRANT, GENERAL PARTNER, NEA

Marti Conger became a patient activist, lobbying the FDA for changes in its regulatory practices, after she faced a similar situation. Conger, who was severely debilitated by cervical disc disease, was forced to travel to England to receive the treatment she and her doctor believed would provide the best results. "I couldn't believe I couldn't get the best treatment in my own country," she said. "Finally, I decided my only solution was to find a foreign surgeon with expertise implanting the devices my physician and I deemed most appropriate—even though the devices were made 40 miles from my U.S. home." Conger paid for her surgery with money from her small savings, as well as gifts and loans.

Conger considered herself a voice for millions of U.S. patients who, in her words, "are needlessly suffering, deteriorating, and sometimes dying while they wait for the FDA"—even though the products they need are sometimes widely available out-of-country and with proven track records. She elaborated:

> "I appreciate [the FDA's] need to protect patients. However, 'absolute assurance' is not a reasonable expectation, as no two bodies are the same. Verify that the product is safe and will function as designed, and then let the patient and doctor make the decision."
>
> — MARTI CONGER, PATIENT ACTIVIST

Conger is lobbying the FDA to accept the regulatory findings of other, trusted nations with strong safety track records (e.g., Europe, Australia, and Japan) or, at a minimum, to "fast track" products that have been cleared/approved in these countries and then monitor them through postmarket studies.

Ross Jaffe, managing director of Versant Ventures, raised an important question for the FDA. "In trying to protect us from things that might not be safe, are we missing out on products that could be very effective?" he asked. By attempting to eliminate safety risks to patients, it is possible that the agency is inadvertently limiting the patient benefits that new technologies can deliver. To truly act in the best interest of patients and the public health, a more holistic perspective is needed. Safety is one important consideration, but there are other equally critical factors to consider. For instance, regulators must take into account the value associated with providing innovative treatments to patients who otherwise might not have any remaining, acceptable options.

IMPLICATIONS TO U.S. MEDTECH INNOVATORS, INVESTORS, AND EMPLOYEES

Since 2008, total annual venture investment in the medtech field has declined by $1 billion.[27] One reason for this dramatic decrease is the global economic downturn, which began in 2008 and intensified in 2009. However, innovators and medtech investors report that there are other factors contributing to this decline, including the changes that have occurred in the U.S. regulatory environment over the last several years.

Less transparent and predictable regulatory processes discourage investors from putting their money into medtech companies. This effect is amplified during an economic downturn when less overall capital is available to medtech venture capitalists and the start-ups they fund. Dr. Paul Yock, a renowned innovator and the director of Stanford University's Program in Biodesign, explained the phenomenon:

> "The development of a new technology of any type is a difficult and fragile process, and the development of a medical technology is a more fragile process still. A major reason for that is regulation. There's a balance that we've gotten reasonably right over the years with being careful about innovation but not stifling it with regulation. But now we have a much more conservative approval process, combined with an economic crunch. Unfortunately for innovators, those two factors can come together to take the gas out of innovation."
>
> — PAUL YOCK, MD, PROFESSOR OF MEDICINE, STANFORD UNIVERSITY

Multiple investors confirmed that the escalating cost of bringing medical devices to market is causing funds to flow out of the medtech sector and into other industries where regulation potentially does not exist (or is not perceived as such a significant barrier). As the survey showed, the average cost of taking a product through 510(k) clearance is $31 million, and the average cost of getting a product through PMA approval is $94 million (excluding reimbursement and sales/marketing activities). Hank Plain, a partner with Morgenthaler Ventures, pointed out how much these costs have increased:

[27] According to data provided by NVCA.

> "When I first started as an entrepreneur in the early 1990s, the amount it took to get a product all the way through a PMA was $30-40 million dollars, which is now what it takes to do a 510(k). So we're seeing a doubling of the cost in a tighter economic environment and with less money available in venture capital."
>
> — HANK PLAIN, PARTNER, MORGENTHALER VENTURES

Historically, investment returns in the device industry are relatively small compared, for example, to those in the biotech and pharmaceutical industries. According to data from the Windhover Strategic Transactions database, approximately 50 percent of medical device exits (for which values were reported) are under $100 million; 75 percent are under $150 million.[28] In cases where the cost of getting to market approaches the average exit value, and given the fact that only four out of every 10 medical technology investments is considered successful,[29] the medtech funding equation under these regulatory conditions is crossing into a domain that is no longer viable.

Importantly, as the survey quantified, FDA-dependent product development stages account for a full 77 percent of the cost of bringing a 510(k) product to market and 79 percent for a PMA, so the effect of regulation on this issue should not be underestimated. As David Cassak, managing director of Windhover Information, described:

> "We've already hit that point where innovators and investors look at the regulatory pathway and say, 'This new technology could be meaningful and could be helpful to patients, but we just can't even take a chance on it.'
>
> — DAVID CASSAK, MANAGING DIRECTOR, WINDHOVER INFORMATION

Stated another way, the burden of an increasingly difficult and costly regulatory path is not just felt by the companies that are ultimately able to bring their technologies to market. This burden can actually serve as a deterrent that keeps innovators from developing their good ideas into company-backed products. As the rate of FDA submissions continues to decline, patients are being negatively impacted as they are denied the opportunity to experience the life-enhancing benefits of technologies that are never developed into products that can be brought to market.

[28] Data provided by David Cassak, managing director of Windhover Information.
[29] According to data provided by NVCA.

At the same time that potential rewards in the industry have diminished with rising regulatory costs and approval timelines, medtech risks have also increased. Uncertainty about FDA expectations has become so great that the regulatory process is often characterized as a "moving target." "In our business, what we like to do is try to manage risk," explained Drant. "If you're aware of what a risk is, you can oftentimes manage it adequately and appropriately. But if the FDA keeps moving the goalpost, it's incredibly hard to manage that risk."

Medtech innovators require greater transparency and predictability from the FDA to help bring the risk/reward equation back into alignment. Jaffe commented:

> "The key issue in my mind is to have a system that can be more efficient, consistent, and predictable in the regulation of devices. That involves having better training of reviewers, better, more up-to-date clinical experts at the FDA who understand the state of the art in what's going on within a specialty, and a process of open and frequent communication between companies and the FDA so we can resolve issues in a reasonable way and move products forward more quickly."
>
> — ROSS JAFFE, MD, MANAGING DIRECTOR, VERSANT VENTURES

Innovators also expressed the desire to be able to meet with the FDA at the start of a medtech product development project, agree on a meaningful clinical trial strategy, and then execute against it with some reasonable assurance that the agency would honor its agreement. Without such changes, the best and brightest talent in the field will potentially start moving to other technology domains, as venture investors are doing, which could ultimately lead to fewer life-enhancing or life-saving devices being developed to meet patient needs.

IMPLICATIONS TO THE U.S. ECONOMY

Until recently, device innovation has largely been a U.S. phenomenon—the most important new technologies were invented here, and commercializing them in the sizable U.S. market was at the core most medtech company strategies. However, as medtech hurdles have climbed and available funding has declined, device companies are considering alternative strategies that are less U.S.-dependent. Unfortunately, as described, this means that many new technologies are reaching U.S. patients later than patients in other geographies. It also suggests that the United States is at risk of losing its premier position at the center of the global medtech innovation ecosystem. As this epicenter shifts, the U.S. economy will be negatively impacted as jobs are moved overseas.

According to Plain, "Every company that I'm involved with now has a European strategy. Ten years ago, many of those companies would have been 100 percent focused on the U.S. for their clinical trials and their product launches. But now what we're seeing is that it's completely reversed—Europe is the first area of focus and, in some cases, it's the only focus." As medtech companies become begin targeting patients and markets outside the U.S., the value of the products they produce and the jobs they create will follow. As Dr. Rodney Perkins, a clinical professor of surgery at Stanford University and a founder of multiple medical device companies, pointed out:

> "In previous decades, we shipped manufacturing jobs offshore. Now we're shipping knowledge worker jobs abroad. Once you export innovation jobs, those jobs won't come back. We need to balance adequate regulatory scrutiny with the rapidly increasing innovation cycle."
>
> — RODNEY PERKINS, MD, CLINICAL PROFESSOR OF SURGERY, STANFORD UNIVERSITY

Despite the fact that U.S. politicians are calling for increased innovation and the high-quality, high-salary jobs associated with innovative industries, survey respondents verified in their comments that medtech jobs are moving offshore. For instance, one participant reported that his device company had recently set up overseas operations, firing 19 employees in the U.S. and hiring 12 in Europe. Next, the company planned to shut down its U.S. production facility and move another 30 to 40 manufacturing jobs to Europe. In this particular example, all future growth was also planned overseas. Keeping in mind that every direct medtech job is indirectly responsible for another 4.47 jobs in the national economy,[30] the effect on U.S. employment could be sizable.

[30] See "State Impacts of the Medical Technology Industry," op. cit., p. 12.

While the needs of an industry or the economy at large should never be prioritized over patient safety, it is not clear that the current regulatory obstacles to U.S. market entry truly contribute to the protection and promotion of public health. Given the dire economic condition of the U.S., the trend toward creating exceptional barriers for one of the few remaining industries in which our country is still a leader should be a significant cause for concern.

LOOKING FORWARD

Our nation currently faces unprecedented challenges in almost every sector of the economy. However, to individual citizens, nothing is more important than their own health and welfare, as well as the health and welfare of their families. Regulators and innovators have an important responsibility to protect and advance public health, and to maintain the balance between risks and benefits for the patients they serve. In doing so, the patient must remain first and foremost in our minds at all times. Patients can be harmed if unsafe medical technologies reach the market, but they are also harmed when important innovations are not available to treat their medical conditions.

The data presented in this report present a troubling picture of the state of medical device regulation (and its effect on innovation and the advancement of public health) under current FDA policies and practices. The survey results also indicate that the pendulum may have swung too far in one direction and balance again needs to be restored.

As noted, the changes at the FDA that have transpired over the last several years (and that have accelerated in the last two years) have largely been driven by perceived safety concerns. Yet, other than isolated examples and anecdotes, no definitive data has been presented to justify such significant and sweeping adjustments. During this period, regulatory processes in Europe have remained relatively constant, making them a valuable comparator for our own regulatory performance in the U.S. It is clear from the data that the European regulatory process is more predictable, reasonable, and transparent. This system also allows companies to make safe and effective new medical products available to patients more quickly, and at a lower cost. The reasonable question has been raised (and requires an answer) whether greater regulatory efficiency in the EU has been achieved at the expense of patient safety. However, no information is available to date to suggest that patient safety in Europe has been compromised. If the same devices become available in U.S. following their European approval only after extensive delays and additional costs are accrued, we must evaluate whether the U.S. premarket regulatory process is truly contributing to the advancement and promotion of the public health, or if it is actually restraining it.

Today, as we face substantial concerns regarding the cost of healthcare, we also must acknowledge that a substantial number of important patient needs still remain unaddressed. A solution to both of these problems cannot be achieved by delaying new innovations and cost-effective treatments. To truly promote the public health, the FDA must impose reasonable regulatory requirements on new innovations, implement more balanced requirements for premarket and postmarket clinical data, and go back to leveraging market forces to reward technology that presents the greatest value to patients. Only then will the most effective advances in medical care be developed and delivered promptly to American patients; and only then will the public health and our economy be best served.

DISCLOSURES

Financial, logistical, and intellectual support for the survey and this report was provided by the Medical Device Manufacturers Association (MDMA), the National Venture Capital Association (NVCA), ExploraMed, California Healthcare Institute, AdvaMed, Mich BIO, MassBIO, PA Bio, Life Science Alley (Minnesota), MedTech (New York), Colorado Bioscience Association, Florida Medical Manufacturers' Consortium, Washington Bio, NEA,and The Foundry.

The study was conducted by Dr. Josh Makower and Aabed Meer. Makower is employed as a Venture Partner at NEA, the CEO of ExploraMed Development, and a Consulting Professor at Stanford University. He also serves on the board or as a consultant to several medical device companies. Aabed Meer is a student at Stanford University pursuing an MD and an MBA concurrently. He worked as a summer associate to conduct the study. Lyn Denend, a research associate at Stanford University, was hired to assist in developing this report.

PricewaterhouseCoopers LLP independently verified the data and analysis presented in the report. The views expressed in the Discussion section reflect the perspectives of the authors, the study participants, and select medtech industry representatives who were interviewed by the authors after reviewing the study results.

Mr. PITTS. The chair thanks the gentleman; recognizes Mr. Deem for 5 minutes.

STATEMENT OF MARK DEEM

Mr. DEEM. Chairman Pitts, Ranking Member Pallone, and members of the subcommittee, thank you for having me here today.

My name is Mark Deem. A biomedical engineer by training, I spent 23 in medical device research and development. Today, I am a partner in a medical device incubator called the Foundry. Our job is to partner with physicians to investigate unmet clinical needs and to invent and develop technologies to create superior patient outcomes.

Over the past 12 years, we have founded, funded, staffed, and run 14 startups. We have raised over $700 million in venture capital. We are inventors on over 250 issued and pending U.S. Patents, and we have employed over 500 people.

Because of these startups, patients who 10 years ago would have had major open heart surgery for cardiac valve disease can now undergo a 1-hour catheter based procedure to have their valve repaired.

Patients who would have been sent to a rehab facility after suffering a stroke to simply hope for the best can now have the blood clot responsible for that stroke removed using a tiny device threaded through their arteries.

Patients with drug-resistant hypertension can undergo a 30-minute procedure that lowers their blood pressure by 3 to 5 times by what drugs can achieve.

Startups are responsible for a huge percentage of the paradigm-shifting breakthroughs in medical care. We are the most fragile end of the medical device ecosystem, and we are struggling. Over the last 2 years, funding for new startups has dropped by almost 50 percent, down from 118 new companies in 2008 to 60 in 2010.

Delays and unpredictability at the FDA are one of the primary risk factors impacting this investment. Over a similar time period, the average time to PMA approval increased by 75 percent; and many of those companies never get there at all.

In 2000, we—emphasis medical to convert an extremely morbid open chest surgery to treat emphysema to a noninvasive scope-based procedure. Eight years and over $75 million of investment having met the clinical trial endpoints, the FDA denied approval for the therapy and recommended continuing on to new studies.

In the face of these moving targets, the board voted to shut the company down in 2009. Forty employees lost their jobs, and the assets were sold at auction. The technology continues to treat patients overseas safely and effectively today.

Also in 2000, we started a company named Satiety to develop a non-invasive, scope-based technology to reduce stomach volume and to treat morbid obesity and diabetes. Ten years and over $80 million of investment later, having met the trial endpoint but while still collecting long-term follow-up, we learned that the FDA was holding companies to a different standard than the ongoing study was constructed to demonstrate. Given past experience, the writing was on the wall for a request for new studies. Just before Christ-

mas of 2010, 37 entrepreneurs lost their jobs as we shut that company down as well.

Today, it is also harder than ever to even get a trial started in the U.S. In 2002, we started Exstent to develop a next-generation, drug-eluding stent. Starting in 2004, we worked with the agency to plan a trial, finally submitting an I.D. in 2007. For 2 years, the agency requested more and more data, ultimately requiring an animal study in pigs with a 2-year follow-up. At the time, Exstent had data from European studies with 1-year follow-up on 220 patients, 2-year follow-up on 100 patients, and 3-year follow-up on 30 patients.

While certainly nobody would consider U.S. patients as guinea pigs, there is no justification for ignoring that kind of data. Could 20 pigs in Michigan really provide more significant data than hundreds of patients in Europe?

Finally in May of 2009, conditional I.D. Approval was granted to Exstent. But by then the company was out of money and was being sold at auction. Over 200 people lost their jobs. Today, development of that technology continues in China and Switzerland.

Experiences like these have led us to fundamentally rethink how we operate. Given the relative stability and predictability of the CE system, we are no longer structuring our companies for first commercial release in the U.S. We develop our products here and then run the same large, multi-center, randomized trial overseas that we would have conducted in the U.S. We then commercialize in the EU while we decide when and if to approach the FDA. As a result, as you have heard, the available of new therapies in the U.S. Can lag the EU by up to 4 years.

We recognize the challenges facing the FDA, and we do value its mission to protect and preserve public health. But we need consistency and clarity to help the FDA achieve its other mission of fostering innovation. A recent study by the Boston Consulting Group shows the EU's safety record is essentially identical to that of the U.S.

So if we are not increasing safety, why should we be satisfied with a system that is driving investment, innovation, and jobs overseas? Why should we be satisfied with a system where U.S. patients wait 4 years longer for access to care that was pioneered in the U.S.? Because the sad fact is many of those patients simply will not live that long.

[The prepared statement of Mr. Deem follows:]

Testimony of Mark Deem

Partner

The Foundry

House of Representatives Energy and Commerce Committee

Subcommittee on Health

"Impact of Medical Device Regulations on Jobs and Patients"

Thank you for inviting me to speak to you today. My name is Mark Deem. A biomedical engineer by training, I have spent 23 years in early stage medical device research and development.

Today, I am a partner in a medical device company incubator called the Foundry. Our job is to partner with physicians to investigate significant unmet clinical needs, and to then invent and develop technologies to better treat patients suffering from those diseases. Over the past 12 years we have founded, funded, staffed and run over a dozen medical device startup companies. We have raised over $700 million in venture capital. We are inventors on over 250 issued and pending US patents and at their high points, our companies employed over 500 people.

Each company that we start focuses on treating a specific disease or condition that improves the lives of patients, improves public health and reduces health care costs. In a number of cases we have studied existing surgical procedures and pioneered ways to replicate the results of those surgeries without making an incision.

Because of the efforts of my partners and I and the teams we have built, patients who 10 years ago would have had major open heart surgery for cardiac valve disease can now undergo a one hour catheter based procedure to have their valve repaired.

Patients who suffer strokes when blood clots become lodged in their brains, who ten years ago would have been sent to rehabilitation facilities to hope for the best, today can have that clot removed with a tiny device threaded into the arteries in their brains. Patients who present unable to speak or move have walked out of the hospital after this procedure.

Patients with uncontrolled drug resistant hypertension can undergo a 30 minute procedure which lowers their blood pressure by 3-5 times what most hypertension medications can achieve.

I am speaking to you today because those of us who operate on the most fragile end of the medical device ecosystem, the startups, are struggling. Startups are responsible for a huge percentage of paradigm-shifting breakthroughs in patient care. We exist for our patients, but we live on venture capital.

According to reports by Price Waterhouse Cooper and the National Venture Capital Association, between 2007 and 2010, venture capital investment in the medical device sector declined by over 37%. Funding for new startups dropped from 118 new companies in 2008 to 60 in 2010 according to the Dow Jones Venturesource. The primary risk factor impacting investment is the unpredictability of and delays by the FDA. This concern is justified - over the same time period the average time to approval for a PMA device increased by 75%. And many companies never get through the process at all.

And that is the good news – those companies actually obtained approval. There are many examples of the following scenario:

- A company works with the FDA to structure a clinical trial with specific endpoints
- The trial is conducted over 3-5 years at costs of $50m or more
- Clinical trial endpoints are met only to have the FDA change the metrics and expectations and request a new trial based on those new expectations

Based upon experience, companies and investors have little reason to believe that the outcome will be any different the next time around. Investors withdraw support, companies shut down, jobs are lost, and patient care suffers.

These experiences have led us to fundamentally rethink how we operate. Given the lack of predictability in the US, and the relative stability and predictability of the CE mark system, we are no longer structuring, staffing or operating our companies for first commercial release in the US. We develop our products here, and then run the same large, multicenter randomized trials we would otherwise have conducted in the US overseas. We are then staying there to commercialize the products while we decide when and if to approach the FDA.

As a result, where earlier this decade PMA products were approved on average about a year earlier in the EU, today that is up to four years.

We recognize the challenges and hard work FDA has before them – we value the FDA and its mission to protect and preserve public health. However, we need consistency and clarity to help the FDA achieve its mission of fostering innovation. If it were clear that a fundamentally longer and more complex FDA process really was providing superior safety for our patients, perhaps our complaints would be moot. But the recent study from the Boston Consulting Group shows that the EU safety record is essentially identical to that of the US.

So if we are not increasing safety, why should we be satisfied with a system that is driving investment innovation and jobs overseas? Why should we be satisfied with a system wherein US patients wait up to 4 years longer for access to care that was pioneered in the US? Because the sad fact is, many of those patients simply will not live that long.

Mr. PITTS. The chair thanks the gentleman and recognizes Dr. Redberg for 5 minutes.

STATEMENT OF RITA REDBERG, M.D.

Dr. REDBERG. Thank you, Chairman Pitts, Chairman Upton, Ranking Member Pallone, Ranking Member Waxman, and others of the subcommittee for this invitation to present some of our work on medical devices.

I am Rita Redberg. I am a professor of medicine and full-time faculty member at the University of California, San Francisco Medical Center in the Division of Cardiology. I am also the chief editor of the Archives of Internal Medicine, a well-respected peer-reviewed medical journal which publishes much research in the area of internal medicine as well as in medical devices. I was a Robert Wood Johnson Health Policy Fellow in the office of Senator Orrin Hatch, and I am currently a member of the FDA Cardiovascular Device Expert Panel as well as the California Technology Assessment Forum.

As a practicing cardiologist, I am very grateful for the advances in medical technology that have allowed me to take better care of my patients every day. However, I have great concerns that many high-risk devices that are reaching the market today are doing so without the benefits of clinical trials which are essential to assure safety and effectiveness for my patients.

Although the 501(k) process was logical and well-intentioned when introduced in 1976, it has in no way kept up with the increased number and complexity of medical devices now available today, particularly in my own field of cardiology as well as in orthopedics.

Unfortunately, although a new device sounds very exciting and glamorous, it cannot be said to be innovated unless it has been shown in a well-done clinical trial to have actual benefit for patients. No matter how innovative a device is, if it is not showing benefit for patients, it is not—I will consider it innovative, and it can't be considered to be beneficial.

Unfortunately, we now have a process where more high-risk devices are going through a 501(k) clearance than are going through the original PMA process. The GAO report in 2009 entitled "FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved Through the Most Stringent Premarket Review Process" found that less than 1 percent of all new devices go through the PMA process. That was not the intent of Congress; and, at the time, FDA resolved to either reclassify these high-risk devices to a lower-risk class or to go through an original premarket approval process. Unfortunately, that has not yet happened.

I want to give you one example of the inferior vena cava filter. This was published in the Archives of Internal Medicine. The Bard Recovery and inferior vena cava filter and G2 device were approved by the FDA pursuant to the 501(k) process. The filter is an umbrella-like device that is put in the main vein in the heart in order to trap clots. This device was investigated by surgeons, including Dr. William Nicholson and colleagues in Pennsylvania, because they noted that several patients of theirs who had this device were coming back in with severe chest pain and shortness of breath.

Upon investigation, they discovered that this device was fracturing and moving to other parts of the body, including the heart, causing puncture of the heart and severe complications. These doctors took it upon themselves to investigate all of the patients at their hospital that had received this device over the last 5 years and found that fully one in four of one type and one in eight of the other type of this filter had fractures. They published these findings as well as notified the FDA.

In my own research on this device, I was shocked to discover that this clearly high-risk implanted device had gone through FDA 501(k) clearance without the benefit of any clinical trial data; and, in fact, there is no randomized data to show that inferior vena cava filters are superior to other methods for treatments of blood clots and prevention of recurrent of pulmonary emboli.

The FDA on the day we published these studies on August 9 last year issued a warning reminding physicians to retrieve these filters because they were meant to be put in and then removed. However, less than 7 percent of all of these filters are currently retrieved.

When I investigated on why the FDA waited 5 years and 921 adverse events to release this morning, I learned that the FDA did not know there were so many serious adverse events because, unfortunately, the computer systems available are arcane and don't allow for real-time monitoring; and so I think that, in order for the FDA to fulfill its mission of protecting the public safety, the FDA needs increased resources and staffing.

We heard that the medical device industry is $135 billion a year in products that are currently covered by Medicare as well as private insurance. In contrast, the Center for Devices and CDRH receives a small budget of $272 million to do all of the premarketing as well as post-marketing surveillance of this huge device industry.

So I think to allow the FDA to fulfill its mission to ensure safety and effectiveness, and that includes adequate premarketing and post-marketing data, we need to give the FDA adequate resources to do so.

Thank you so much.

[The prepared statement of Dr. Redberg follows:]

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Testimony of Rita F. Redberg, MD, MSc.
Subcommittee on Health
House Committee on Energy and Commerce
February 17, 2011

Thank you Chairman Pitts, Chairman Upton, Ranking Member Pallone and Ranking Member Waxman and other distinguished members of the Health Subcommittee for this invitation to present 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 and also 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 general internal medicine. Much of my recent research has concerned the appropriate and optimal use of medical technology in patient care, and the journal frequently publishes articles related to use of medical devices.

I was a Robert Wood Johnson Health Policy Fellow and worked in the office of Senator Orrin G. Hatch (R-Utah). I am also a member of the American College of Cardiology Science and Quality committee, and I have served on numerous scientific writing groups for the American College of Cardiology and American Heart Association concerning medical technology and the appropriate use of medical technology. I have most 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 Cardiology Technology Assessment Forum.

Introduction and overview of 510k

As a practicing cardiologist, I am grateful for the advances in medical technology that have allowed me to take better care of my patients every day. The "510k" approval process has been valuable in allowing speedy approval of low risk devices, such as ECG machines, which have greatly contributed to improved patient care. As you know, the FDA was given responsibility for regulation of devices in 1976. At that time, most devices on the market were low and moderate risk. Indeed, most of the implantable devices we use today were not invented, or even a twinkle in our eye, in 1976. The 510k approval pathway was developed in recognition of the fact that a number of devices then in use already had been shown to be safe; it was decided that such devices, and moderate improvements to such devices, should not have to go through an additional approval process.

Thus, under this 1976 law, products that were "substantially equivalent" to these tried and true low risk devices could be approved by the FDA without new clinical trial data. Although the 510k approval process was logical and well-intentioned, it became a widely used, but in many cases, dangerous, shortcut during the last 10 to 20 years as the number and complexity of medical devices exploded, particularly in the fields of cardiology and orthopedics. In contrast to most devices in the 70's, the newer products pose substantially greater risks – even life-threatening risks – to patients. For example, many new medical devices are permanently implanted in a patient's body and can be moved or changed, it at all, only with great risk to the patient. Congress had directed that such high-risk devices should go through a more stringent approval process (the premarket approval process) or be reclassified as lower risk devices. But this did not happen.

GAO report

In fact, the General Accountability Office in 2009 found that more high-risk devices were being cleared by the 510k approval process than were going through the original premarket approval submission process. (*See* FDA Should Take Steps to Ensure That High-Risk *Device* Types Are Approved through the Most Stringent Premarket Review Process)[1] At that time, the GAO stated that the FDA was inappropriately approving high-risk devices via the 510k process instead of requiring the more stringent premarket approval mechanism. Indeed, *currently less than one percent of all new devices go through the PMA process.* While 510k clearance is appropriate in circumstances where low- and moderate-risk devices are substantially equivalent to previously approved devices, this approval pathway was not intended for, and should not be used for, high risk devices. The increasingly routine use of this inappropriate shortcut approval for numerous high risk devices over the last decade, means that tens of thousands of Americans live with implanted devices of unknown benefit and definite safety risk to their health.

Inferior vena cava filter

This risk, moreover, is not merely hypothetical. For example, the Bard Recovery and inferior vena cava (IVC) filter device, and a related device called the G2, were approved by the FDA pursuant to the 510k process. A filter is an umbrella-like device opened into one of the largest veins of the heart in order to trap clots. This device was investigated by surgeons, including Dr. William Nicholson and colleagues in Pennsylvania, who had noted that several patients at their hospital who had received Bard Recovery filters had returned with chest pain and shortness of breath. The physicians discovered that these devices had fractured apart. Pieces of the devices had traveled and punctured the lining of the heart, causing life-threatening complications of cardiac puncture. These doctors astutely decided to call back all of their patients who had received the Bard Recovery and G2 over the last 5 years to check on their condition. They were shocked to find that in fully a quarter of one type of device, and an eighth of the other type of device, these filters had fractured inside their patient's bodies. Their research led them to notify the FDA of their findings, which were published in the *Archives of Internal Medicine.*[2]

In my own research, I was alarmed to discover that these IVC filters, which were clearly implantable and could cause great harm to these patients, had been approved for use under the 510k mechanism without any clinical trial data. [3] The day that we published Dr. Nicholson's article (August 9, 2010), the FDA issued a warning that they had received 921 adverse event reports about IVC filters since 2005 and reminding doctors that these were approved as "retrievable" devices, and that doctors should be retrieving them. In actual fact, only 7% of all

retrievable IVC filters are ever retrieved. On obvious question arising from this incident is why it took five years and 921 adverse events for the FDA to issue its warning. The reason, I learned, is that until reviewing the *Archives* article the FDA had no idea that there were so many serious adverse events associated with IVC filters. It seems the FDA lacked a real-time system to adequately monitor serious adverse events as they are posted in the FDA databases. These arcane database systems in use at FDA mean that only a small percentage of all adverse events are ever reported to FDA, and those that are reported are not always acknowledged or monitored in any systematic fashion. This is an important example that I want to emphasize. It means that many devices that are causing serious harm have not come to the attention of the FDA and therefore have not yet been recalled. It is very difficult for the FDA to know that a device is causing serious harm and should be recalled, because they are relying on reports from doctors and hospitals that are not necessarily made, and even when they are the FDA does not have the technology to notify them when hundreds of similar adverse reaction reports have been made for a specific device.

So the high-risk recalls listed on the FDA web site are the tip of the iceberg. The IVC blood filters, which are killing patients, would not have lead to a FDA warning on retrieval if it hadn't been for our published article.

The double whammy - limitations in both premarketing data & postmarketing surveillance
These incidents reveal two major problems, in my opinion, that need immediate improvement in the FDA device approval process. First, too many high-risk devices are being cleared by a 510k mechanism without any clinical trial data; and second, after device approval there is little or no post-marketing surveillance that would detect serious adverse events in a timely fashion. The result is that hundreds of thousands – and possibly millions – of Americans are carrying implanted devices with unknown risks and benefits. In 2006 alone, the FDA received almost 3000 reported deaths from medical devices, and that number increased to almost 5,000 in 2009.[4]

Off –label use common for medical devices
What is more disconcerting is that we cannot assure our patients that the benefits of these new devices outweigh the risks, because so many of the devices were approved without the benefit of clinical trial data to show improvement in outcomes. This is especially true when such devices are used for purposes other than for what they are labeled, which occurs in the the vast majority of all device use. For example, the *Archives of Internal Medicine* also published an article showing that only half of the IVC filters are implanted under appropriate indications, where there are known benefits. It is estimated that 80-90% of all cardiac stent use is off-label.

Quality of premarket approval data
Even the clinical data in support of high-risk devices which go through the most stringent pre-market approval pathway needs improvement. Prescription drugs are approved based on clinical trials, and many medical devices need to be held to the same standard. I can't help but wonder why clinical trials are widely accepted by the pharmaceutical industry as essential to ensure patient safety, but not by the device industry. As a result of the industry's reluctance to conduct clinical trials and the FDA's failure to require them, many devices are approved without any clinical data or approved with clinical data showing only a surrogate endpoint. My UCSF colleagues, Dr. Sanket Dhruva, Dr. Lisa Bero, and I looked at the quality of evidence that supported premarket approvals of cardiovascular devices, the most stringent approval pathway for the FDA. Our research, which was published in the *Journal of the American Medical*

Association on December 23, 2009, found that only 27% of all premarket approvals were based on a randomized trial. [5] Only 14% percent of these trials were blinded. A total of less than 7% of all trials to support premarket approval of high-risk devices were done in a randomized, controlled blinded way, which researchers agree is the gold standard for scientific evidence.

Our research further showed that two-thirds of all premarket approval applications are based on a single study. Even that one study need not be from a high quality randomized, controlled or blinded clinical trial. Data may be from trials not in the United States, with short follow up and surrogate endpoints – that is, points that are not clinical meaningful to patients. In summary, while I think it is important to allow and encourage speedy approval of life-saving devices, I think it is critical that we first have high quality evidence that the benefits of these devices will outweigh the risks.

Device Recalls

Of course, the risks are great once you have had a device implanted. Removing an implanted device is risky, if not impossible. This means that it is essential for the health and safety of Americans that we have evidence of benefit that outweighs this risk prior to FDA approval of their device. Clearly, evidence that the device improves health outcomes is only possible from clinical trials. The problems multiply when there are defects in the manufacturing process, such as what happened in the case of several different defibrillator leads. These are the wires that attach to the pacemaker implanted in order to shock your heart if it stops. Defibrillator leads illustrate further problems in the device approval system. Guidant received reports from patients and doctors for three years about problems with its Prizm 2 system before it acknowledged the problem. [6] For example, when another defibrillator lead, the Sprint Fidelis , was recalled on October 15, 2007, hundreds of thousands of Americans had to be notified – and then had to make the difficult decision of whether to undergo a life-threatening procedure to have their lead removed, or whether to live with the unsettling knowledge that their lead may malfunction and cause a serious adverse event, or even death. One such patient was Don Fernbach, a 55 year old accountant, who received an ICD with a Sprint Fidelis lead in April, 2007, which was 2 months after Dr. Hauser's warning to Medtronic that there was a problem, and 1 month after Medtronic issued their "Dear Doctor" letter. On June 30, 2008 his lead failed and he received 21 shocks before a Medtronic tech at the hospital disabled the ICD. His readings indicated that the ICD had been detecting the impending failure for 20 days, yet he had no warning! The FDA had recommended in its recall notice that there be frequent monitoring. Since I already had the monitor, all Medtronic needed to do was let me do a weekly transmission, and their computers would have identified the problem allowing my doctors to act before the ultimate failure.

Supplemental PMAs

The Sprint Fidelis lead was approved through the PMA process, but not as a new product. It was approved in a supplemental PMA as a "similar" product to their earlier leads such as the Quattro, which itself had been approved on a supplemental PMA. In fact, the original PMA was from the early 1990s. The FDA apparently had seen no clinical test results on any Medtronic lead since the original PMA. The 2009 GAO report found that from 2003-2007 there were 217 original PMA and784 supplemental PMAs. More Class III (high risk) devices were given a 510k clearance than went through an original PMA. [7] Clearly, in order to protect the health and safety of Americans we must do as excellent a job as possible in assuring high quality evidence that high-risk devices will be of benefit and that these benefits will outweigh these risks.

Conclusion

I appreciate greatly the value of innovation in helping me to take excellent care of my patients. But it is not in the interest of my patients, or the American public to allow medical devices to get to market without the benefit of high quality clinical studies to demonstrate that they will actually help patients to feel better and even live longer, without causing harm. Devices with no known benefit are now implanted in millions of Americans placing them at great risk for serious adverse events, including death. Such practices are not innovative, they are a threat to public safety. We can avoid, or substantially minimize, this risk through proper use of evidence-based medicine and well-designed clinical tests *before* the devices are approved and clinical registries to track outcomes in real time *after* they are approved.

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[1] GAO Report: "FDA Should Take Steps to Ensure That High-Risk *Device* Types Are Approved through the Most Stringent Premarket Review Process"
GAO-09-190, Jan 15, 2009

[2] Nicholson W, Nicholson J, Tolerico P, Taylor B, Solomon S, Schryver T, McCullum K, Goldberg H, Mills J Schuler B, Shears L, Siddoway L, Agarwal N, Tuohy C. "Prevalence of Fracture and Fragment Embolization of the Bard Recovery and Bard G2 Cava Filters and Clinical Implications Including Cardiac Perforation and Tamponade". Arch Int Med 2010 Nov; 170:1827-31

[3] Redberg RF. "Medical Devices and FDA Approval Process: Balancing Safety and Innovation". Arch Int Med 2010; doi:10.1001/archinternmed.2010.323

[4] Zuckerman D, Brown P, Nissen S. "Medical Device Recalls and the FDA Approval Process". Arch Int Med 2011; doi:10.1001/archinternmed.2011.30

[5] Dhruva SS, Bero LA, Redberg RF. "The Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices". JAMA. Dec 23; 302(24):2679-85

[6] Meier B, "Maker of Heart Device Kept Flaw From Doctors". New York Times, May 24, 2005

[7] GAO Report: "FDA Should Take Steps to Ensure That High-Risk *Device* Types Are Approved through the Most Stringent Premarket Review Process"
GAO-09-190, Jan 15, 2009

Two attachments

[7] Redberg RF. "Medical Devices and FDA Approval Process: Balancing Safety and Innovation". Arch Int Med 2010; doi:10.1001/archinternmed.2010.323

Redberg RF and Dhruva SS. "Medical Devices Recalls: Get it right the first time. Arch Int Med 2011: epub ahead of print

should be educated about this fact so that they have the opportunity to consider having the filter removed.

It is important to recognize that our data represent only a single-center experience. However, 6 different physicians from 3 different specialties implanted the devices that went on to fracture. While our medical center is representative of most large tertiary care hospitals, it is important that our data be corroborated with independent evaluation of implanted devices from other centers. In addition, other brands of IVC filters must be evaluated to determine if our findings are specific to the Bard devices or are a flaw of all such filters.

In conclusion, the prevalence of fragmentation and embolization was found to be high in both the Bard Recovery (25%, 7 of 28) and the Bard G2 (12%, 6 of 52) vena cava filters. Dissemination of these results has a clear benefit for the medical community. Further implantation of these particular devices has been halted at our institution. Educating the medical community and patients on the possibility of device fragmentation and embolization will lead to future patient protection. The optimal approach to the treatment of patients who have already received one of these devices is unclear. Filter fragmentation and embolization might be due to metal fatigue, and therefore its incidence might be directly related to the time that it remains implanted. The decision whether to remove an implanted device will have to be tailored to each individual's particular clinical scenario. It is essential that other medical centers evaluate patients who have received a Bard retrievable filter or any other IVC filter, both for patient safety and to corroborate our single-center findings.

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Author Contributions: Dr W. Nicholson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* W. Nicholson, Goldberg, and Schuler. *Acquisition of data:* W. Nicholson, W. J. Nicholson, Tolerico, Taylor, Solomon, Schryver, McCullum, Mills, Shears, Agarwal, and Tuohy. *Analysis and interpretation of data:* W. Nicholson, Solomon, McCullum, Siddoway, and Tuohy. *Drafting of the manuscript:* W. Nicholson, Schuler, and Shears. *Critical revision of the manuscript for important intellectual content:* W. Nicholson, W. J. Nicholson, Tolerico, Taylor, Solomon, Schryver, McCullum, Goldberg, Mills, Siddoway, Agarwal, and Tuohy. *Statistical analysis:* W. Nicholson and Tuohy. *Obtained funding:* W. Nicholson. *Administrative, technical, and material support:* W. Nicholson, Tolerico, Solomon, McCullum, Schuler, Shears, Siddoway, and Tuohy. *Study supervision:* W. Nicholson.
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REFERENCES

1. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med.* 1998;158(6):585-593.
2. Ferris EJ, McCowan TC, Carver DK, McFarland DR. Percutaneous inferior vena caval filters: follow-up of seven designs in 320 patients. *Radiology.* 1993;188(3):851-856.
3. Poletti PA, Becker CD, Prina L, et al. Long-term results of the Simon nitinol inferior vena cava filter. *Eur Radiol.* 1998;8(2):289-294.
4. Kumar SP, Mahtabifard A, Young JN. Fractured inferior vena cava filter strut presenting as a penetrating foreign body in the right ventricle: report of a case. *J Card Surg.* 2008;23(4):378-381.
5. Saeed I, Garcia M, McNicholas K. Right ventricular migration of a recovery IVC filter's fractured wire with subsequent pericardial tamponade. *Cardiovasc Intervent Radiol.* 2006;29(4):685-686.
6. Hull JE, Robertson SW. Bard Recovery filter: evaluation and management of vena cava limb perforation, fracture, and migration. *J Vasc Interv Radiol.* 2009;20(1):52-60.
7. Lynch FC, Kekulawela S. Removal of the G2 filter: differences between implantation times greater and less than 180 days. *J Vasc Interv Radiol.* 2009;20(9):1200-1209.
8. Cantwell CP, Pennypacker J, Singh H, Scorza LB, Waybill PN, Lynch FC. Comparison of the recovery and G2 filter as retrievable inferior vena cava filters. *J Vasc Interv Radiol.* 2009;20(9):1193-1199.
9. Grande WJ, Trerotola SO, Reilly PM, et al. Experience with the recovery filter as a retrievable inferior vena cava filter. *J Vasc Interv Radiol.* 2005;16(9):1189-1193.

INVITED COMMENTARY

HEALTH CARE REFORM

Medical Devices and the FDA Approval Process

Balancing Safety and Innovation

The use of medical devices has greatly increased during the past decade. Indeed, more than 8000 new medical devices are marketed in the United States annually.[1] The US Food and Drug Administration (FDA) is responsible for assuring the safety and effectiveness of devices prior to and following approval for use in the United States. The FDA classifies medical devices according to risk of causing harm. Class I and II devices are considered to be low risk and approval may be accomplished through a relatively simple "premarket notification" or 510(k) clearance, which does not require clinical data. Class III devices are those consid-

ered high risk; Class III devices generally require a premarket approval (PMA) process that includes clinical data showing safety and effectiveness. When Congress established device classes in 1976, its intent was that all Class III devices eventually would be required to undergo premarket review through the more stringent PMA process.[2(p17)]

Recently, the process for device approval has come under scrutiny owing to the poor quality of evidence supporting the PMAs on which devices have been approved and owing to the large percentage of high-risk devices that bypass PMAs altogether and are approved through 510(k) clearances.[3,4] In particular, despite the surprisingly weak PMA data, a 2009 Government Accountability Office study discovered that the *FDA did not deny approval of a single PMA submission* between 2003 and 2007.[2] Moreover, even though the FDA claims that "most Class III devices require Premarket Approval," nearly 60% of the Class III devices approved during this period failed to undergo the PMA process at all and instead received 510(k) clearances which do not require clinical data.[4] These statistics alone strongly suggest that the FDA's device approval process needs urgent improvements.

In making approval decisions the FDA must protect the public safety without stifling innovation through unnecessary delays in approval. The Critical Path Initiative[5] was launched in 2004 with the goal of shortening the time to approval for new drugs and devices by "developing better evaluation tools like biomarkers and new assays and streamlining clinical trials by modernizing the clinical trial sciences to make trials safe and efficient." The FDA Center for Devices and Radiologic Health has established a Council on Medical Device Innovation. A recent public workshop[6] (June 2010) brought together industry representatives, physicians, and patients and other members of the public in an effort designed, according to the Center Director, Jeffrey Shuren, to "get better devices to patients faster."

Faster approval, however, increases the need for high-quality, reliable data showing safety and effectiveness to support approval. In addition, the collection of *postapproval* data becomes more crucial. This need for long-term follow-up is especially important for high-risk cardiovascular devices, which generally are permanently implanted in patients. However, the longest follow-up for high-risk cardiovascular devices approved via the more stringent PMA process was only a median of 365 days for intracardiac devices and endovascular grafts.[3]

In their study, Nicholson and colleagues report a serious and possibly fatal complication of the popular and widely used Bard inferior vena cava (IVC) filters (Bard Peripheral Vascular, Tempe, Arizona). Three years after receiving an IVC filter, one of the authors' patients presented with pleuritic chest pain and cardiac tamponade as a result of filter fragmentation and embolization of the device. The group thereafter contacted all of their patients who had received Bard Recovery and Bard G2 filters to further investigate the longer-term effects. They found that the filters had fractured in an astounding 25% of patients implanted with the Bard Recovery filter (approved in 2002). For patients implanted with the newer Bard G2 filter (approved in 2005), they found fracturing in 12% of patients. They theorize that the lower rate for the newer filter is due to the shorter indwelling time and predict G2 filter fractures will rise over time. Extrapolating this data for the 65 000 G2 filters that have been implanted suggests that more than 7000 Americans may now be carrying a fractured G2 filter, with the potential to embolize to the IVC and beyond. Moreover, although the devices were approved as retrievable, the data suggest removal is not simple: less than 7% of devices were removed according to the article by Nicholson and colleagues. The safety of removal of the device after long-term use is not well established.

Remarkably, these filters, which are placed inside the IVC, were considered Class II by the FDA—the same risk category of mercury thermometers—and received approval without any clinical data of safety and effectiveness identified in their 510(k) clearances. The only performance data listed in the Bard Recovery Summary (K022236)[7] describes bench testing performed per the FDA document "Guidance for Cardiovascular Intravascular Filter 510(k) Submission." Testing showed that the Recovery filter is substantially equivalent to the Bard predicate device. The Bard Recovery Filter was submitted as a "Special 510K" pursuant to which a manufacturer may "declare conformance to design controls without providing the data." In that case, the manufacturer need only submit a "Declaration of Conformity" with design control requirements. For the Bard Recovery Filter, the only clinical data provided were to support the safety of removing the device and thus a retrievable filter was approved in a subsequent 510(k).[8] Similarly, the G2 filter Summary (K050558)[9] has no clinical data, only a list of similarities to the Bard Recovery filter.

The report by Nicholson et al is a case study showing why the FDA device approval process must be more clearly defined. First, high-risk devices must go through the appropriate approval process adequately supported by reliable data. Manufacturers should not be routinely permitted to circumvent the PMA process for high-risk devices by means of 510(k) clearances. Second, PMAs must be supported by high-quality clinical data showing safety and effectiveness prior to approval of high-risk devices, including such products as valve rings, vascular filters, and other devices that are permanently implanted and can have serious adverse events, including death, after placement.

Fortunately, the FDA appears to be taking action. Among other things, the FDA has asked the Institute of Medicine to review the use of the 510(k) clearance, and a report with their recommendations is expected in spring 2011. In addition, in light of the fact that short-term studies often will miss less common problems, the process for developing and reviewing postmarket data must be significantly strengthened. Currently, required follow-up studies are often not completed, the follow-up data are not publicly available, and even if they are completed, the FDA rarely acts on the findings.

The FDA also has announced a new transparency initiative.[10] Hopefully, this transparency will include requiring that clinical data submitted to the FDA, both in

the application process and postapproval, be publicly available. The FDA also must have authority and the will to withdraw device approvals if postmarketing data requirements are not met *or* if the postmarketing data show safety or effectiveness problems. Mechanisms for collecting postmarketing data must be made user friendly and publicly accessible. Registries such as the National Cardiovascular Data Registry and others are an important step in that direction. Currently, only 5% to 10% of all adverse events are actually reported. We have had many recent reminders that even those adverse events that are reported are not readily publicly available or turned over to the FDA in a timely fashion. The FDA recently sent another 12-page warning letter to Pfizer about delays in reporting adverse events dating back 6 years. The recent Avandia firestorm highlighted the importance of transparency of data. The problem is even more pressing and urgent for devices as seen in high-profile device recalls (Fidelis) as well as the recent Boston Scientific alert of serious problems with some of their implantable cardioverter-defibrillators.[11]

While we all appreciate the potential advantages of medical devices, prudent policy requires high-quality clinical data showing that the benefits outweigh the risks, before and after FDA approval. Holding manufacturers to these standards will enhance, not hinder, innovation and advancement of the science of medical devices.

Rita F. Redberg, MD, MSc
Editor

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Additional Information: Dr Redberg is a member of the FDA Cardiovascular Devices Expert Panel and the California Technology Assessment Forum.

1. Feigal DW, Gardner SN, McClellan M. Ensuring safe and effective medical devices. *N Engl J Med*. 2003;348(3):191-192.
2. US Government Accountability Office. FDA Should Take Steps to Ensure that High-risk Device Types are Approved Through the Most Stringent Premarket Review Process. GAO-09-190. January 2009. http://gao.gov/new.items/d09190.pdf. Accessed July 26, 2010.
3. Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. *JAMA*. 2009; 302(24):2679-2685.
4. Garber AM. Modernizing device regulation. *N Engl J Med*. 2010;362(13):1161-1163.
5. Critical Path Initiative. http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm. Accessed July 26, 2010.
6. Public Workshop: Identifying Unmet Public Health Needs and Facilitating Innovation in Medical Device Development. June 24, 2010. http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212831.htm#agenda. Accessed July 26, 2010.
7. Recovery Filter System. 510(k) Summary of Safety and Effectivenes Information. http://www.accessdata.fda.gov/cdrh_docs/pdf2/K022236.pdf. Accessed July 29, 2010.
8. Recovery Filter System. Abbreviated 510(k). http://www.accessdata.fda.gov/cdrh_docs/pdf3/K031328.pdf. Accessed July 29, 2010.
9. G2 Filter With Femoral Delivery. Traditional 510(k). Summary of Safety and Effectiveness. http://www.accessdata.fda.gov/cdrh_docs/pdf5/K050558.pdf. Accessed July1 29, 2010.
10. Asamoah AK, Sharfstein JM. Transparency at the Food and Drug Administration. *N Engl J Med*. 2010;362(25):2341-2343 Published online May 19, 2010.
11. Boston Sci confirms problems in 3 ICD models. http://www.reuters.com/assets/print?aid=USN2222410920100722. Accessed July 26, 2010.

Mr. PITTS. The chair thanks the gentlelady and recognizes Dr. Nissen for 5 minutes.

STATEMENT OF STEVEN E. NISSEN, M.D.

Dr. NISSEN. Thank you for the opportunity to testify today.

My name is Steven E. Nissen, M.D. I am chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic. My testimony does not reflect the views of the Cleveland Clinic.

I agree with the underlying premise of these hearings. For decades, the American medical products industry has been responsible for innovations that have saved lives, reduced suffering, and sometimes even lowered medical costs. I also agree that this industry creates high-quality jobs that contribute to the Nation's economic health.

The dilemma proposed by today's hearings is how to best promote innovation, while protecting the health of the American people. Medical devices are regulated via an antiquated regulatory system originally devised in 1976 that employs two very different pathways to market.

Premarket approval is a rigorous standard similar to the approach used to regulate pharmaceutical products. The 501(k) provision allows products to be cleared for market if they are deemed substantially equivalent to devices already marketed, many before 1976. Surprisingly, 35 years later, the 501(k) pathway is now used for 98 percent of all medical devices. 501(k) cleared devices rarely undergo any testing in patients, and manufacturing facilities are not subject to FDA inspections. Often, new devices are very dissimilar to previously marketed medical products, use different materials and manufacturing processes, and have different intended uses.

The abbreviated 501(k) process was never intended for Class III medical devices, products used for life-supporting or life-sustaining indications. However, FDA has sometimes cleared such devices for market using the 501(k) provision, a policy that was sharply criticized by the GAO in a 2009 report.

In recent years, several high-profile withdrawals of medical devices have resulted in serious injuries or death. In a particularly poignant example, a faulty lead used in an implantable defibrillator frequently failed, resulting in inappropriate shocks or, worse, a failure to function during a cardiac arrest, resulting in death.

When this problem was identified, patients were presented with an agonizing choice: to undergo an operation to remove the defective device or take their chances that it wouldn't fail when needed to save their life.

An artificial hip joint used in 13,000 patients failed rapidly, often releasing toxic metal debris which sickened thousands of patients. Again, patients faced the choice of a painful and risky operation or accepting the possibility of serious health consequences.

We recently analyzed all 113 high-risk medical device recalls from 2005 to 2009 of products FDA deemed could cause serious injury or death. Surprisingly, 71 percent of these high-risk recalls involved devices initially cleared using the 501(k) process. Only 19 percent had undergone full PMA approval.

This finding represents a paradox. If by Federal regulations high-risk devices should not be cleared using the 501(k) provision, there should almost never be recalls of such devices for life-threatening defects.

The total number of devices recalled in this interval exceeded 112 million. According to FDA data, more than 2,000 deaths are reported each year from failure of medical devices, rising to nearly 5,000 in 2009. These statistics illustrate the need for a balanced approach to medical device regulation.

Although we all want to stimulate innovation and job creation, we cannot allow deregulation to place the American public at risk for serious health consequences from defective products. A more nuanced approach to device regulation would appropriately balance the need for timely approval with patient safety.

Components of reform should include: a more accurate definition of a high-risk device which takes into account the likely risks if the device is defective; an intermediate regulatory category more rigorous than 501(k) but short of a full PMA process for moderate risk devices; and, very importantly, better funding for the FDA Center for Devices to enable timely but thorough evaluation of the risks and benefits of medical devices.

Thank you again for the opportunity to appear here today.

[The prepared statement of Dr. Nissen follows:]

Testimony to the House Committee on Energy and Commerce (Health Subcommittee)

Title of Hearing: "Impact of Medical Device Regulations on Jobs and Patients"

Date of Hearing: February 17, 2011

Witness: Steven E. Nissen MD

My name is Steven E. Nissen, M.D. I am Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic and former President of the American College of Cardiology (ACC). My testimony does not reflect the views of either the Cleveland Clinic or the ACC.

I agree with the underlying premise for these hearings. For decades, the American medical products industry has been responsible for innovations that have saved lives, reduced suffering, and sometimes even lowered medical costs. I also agree that this industry creates high-quality jobs that contribute to the nation's economic health. For these reasons and many others, strengthening a vibrant and vital medical device industry is an important national priority.

The dilemma posed by today's hearings is how to best promote innovation, while protecting the health of the American people. Medical devices are regulated via an antiquated regulatory system originally devised in 1976 that employs two very different pathways to market.

Premarket Approval is a rigorous standard similar to the approach used to regulate pharmaceutical products, often involving careful testing in patients with a full regulatory review. The 510(k) provision allows products to be "cleared" for market if they are deemed "substantially equivalent" to a "predicate" device already marketed, many before 1976. Surprisingly, 35 years later, the 510(k) pathway has become the primary approach used by FDA to clear products for market, now utilized for 98% of all medical devices. Devices approved under the 510(k) provision rarely undergo any testing in patients and manufacturing facilities are not subject to FDA inspections.

Often, new medical devices are very dissimilar to previously-marketed products, use different materials and manufacturing processes, have different mechanisms of action and have different intended uses. It is no longer reasonable to compare modern medical products with devices marketed as long as 35 years ago.

The abbreviated 510(k) process was never intended for use for clearing Class III medical devices, defined by the Code of Federal Regulations as products used for life-supporting or life-sustaining indications, for preventing impairment of human health, or presenting a potentially unreasonable risk of illness or injury. However, FDA has sometimes cleared Class III devices for market using the 510(k) provision, a policy that was sharply criticized by the GAO in a January 2009 report.

In recent years, several high profile withdrawals of medical devices have resulted in serious injuries or death. In a particularly poignant example, a faulty lead used in an implantable defibrillator frequently failed, resulting in inappropriate shocks or worse, a failure to function during a cardiac arrest, resulting in death. When this problem was identified, patients were presented with an agonizing choice, to undergo an operation to remove the defective device, or take their chances that it wouldn't fail when needed to save their life.

Automated external defibrillators (AEDs) were approved under the 510(k) provision. These devices are used to permit bystanders to resuscitate victims of cardiac arrest. During the last 5 years,

FDA has received more than 28,000 reports of AED failures resulting in hundreds of deaths. Many AED devices were recalled for manufacturing defects.

An artificial hip joint used in 13,000 patients rapidly failed, often releasing toxic metal debris, which sickened thousands of patients. Again, patients faced the choice of a painful and risky repeat operation or accepting the possibility of serious health complications from this faulty device.

Colleagues at the National Research Center for Women and Families, Dr. Diana Zuckerman and Paul Brown, and I analyzed all 113 high-risk medical device recalls from 2005-2009. FDA designated these recalls as high risk because the devices could cause serious injury or death. Surprisingly, 71% of these high-risk recalls involved devices initially cleared using the 510(k) provision. Only 19% had undergone full PMA approval. 7 % were intentionally exempt from any FDA review because they were considered so low risk.

This finding represents a paradox. Federal regulations require devices used to support or sustain life to undergo a full PMA approval process. By law, these life-sustaining devices should not be cleared using the 510(k) provision. Yet 71% of recalls for defects that could "cause serious health problems or death" were originally approved using the 510(k) pathway.

The total number of devices recalled during this interval exceeded 112 million. According to the FDA data, there have been more than 2,000 deaths reported each year from medical devices, rising to almost 5,000 in 2009. The number of annual injuries is much higher –over 100,000 in 2006, according to the FDA statistics.

These findings illustrate the need for a balanced approach to approval of medical devices. Although, we all want to stimulate innovation and job creation, we cannot afford to allow deregulation to place the American public at risk for serious health consequences from defective products not adequately studied prior to human use.

I believe that we need a more nuanced approach to device regulation that appropriately balances the need for timely approval with patient safety. Components of reform should include:

1) A more accurate definition of a high risk device, which takes into account the likely risks if the device is defective.
2) An intermediate regulatory category more rigorous than 510(k), but short of a full PMA process, for moderate risk devices.
3) Better funding for FDA Center for Devices to enable timely, but thorough, evaluation of the risks and benefits of medical devices.

ORIGINAL INVESTIGATION

ONLINE FIRST | HEALTH CARE REFORM

Medical Device Recalls and the FDA Approval Process

Diana M. Zuckerman, PhD; Paul Brown, BS; Steven E. Nissen, MD

Background: Unlike prescription drugs, medical devices are reviewed by the US Food and Drug Administration (FDA) using 2 alternative regulatory standards: (1) premarket approval (PMA), which requires clinical testing and inspections; or (2) the 510(k) process, which requires that the device be similar to a device already marketed (*predicate* device). The second standard is intended for devices that the FDA deems to involve low or moderate risk.

Methods: We analyzed the FDA's high-risk List of Device Recalls from 2005 through 2009. Using FDA data, we determined whether the recalled devices were approved by the more rigorous (PMA) process, the 510(k) process, or were exempt from FDA review.

Results: There were 113 recalls from 2005 through 2009 that the FDA determined could cause serious health problems or death. Only 21 of the 113 devices had been approved through the PMA process (19%). Eighty were cleared through the 510(k) process (71%), and an additional 8 were exempt from any FDA regulation (7%). Cardiovascular devices comprised the largest recall category, with 35 of the high-risk recalls (31%); two-thirds were cleared by the 510(k) process (66%; n=23). Fifty-one percent of the high-risk recalls were in 5 other device categories: general hospital, anesthesiology, clinical chemistry, neurology, or ophthalmology.

Conclusions: Most medical devices recalled for life-threatening or very serious hazards were originally cleared for market using the less stringent 510(k) process or were considered so low risk that they were exempt from review (78%). These findings suggest that reform of the regulatory process is needed to ensure the safety of medical devices.

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IN 1938, WHEN THE US CONGRESS first mandated that medical products demonstrate safety and effectiveness, the law applied only to drugs, not to medical devices. Congress did not give the US Food and Drug Administration (FDA) the authority to regulate all medical devices until 1976, when it amended the Food, Drug, and Cosmetics Act in response to deaths

See Invited Commentary at end of article

and infertility caused by the Dalkon Shield and other contraceptive intrauterine devices. Congress and the FDA weighed 2 competing goals during passage of this legislation: providing "the public reasonable assurances of safe and effective devices"[1(p1339)] while avoiding "overregulation"[1(p1339)] of the industry.

The 1976 law included a premarket approval (PMA) process for devices that is similar to the new drug application process used for pharmaceuticals. Submissions for PMA require extensive testing, including "valid scientific evidence"[2(p2)] that "provide[s] reasonable assurance that the device is safe and effective for its intended use."[2(p2)] The PMA process was developed as the approval pathway for medical devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[2(p2)]

Thousands of devices were already marketed in 1976, so Congress included an alternative pathway to the PMA known as the 510(k) provision, which was intended to provide a less burdensome route to enable newer versions of existing devices to enter the market. The 510(k) pathway did not require clinical trials or manufacturing inspections to demonstrate safety and efficacy. Instead, the sponsor was required only to demonstrate that the device was *substantially equivalent* in materials, purpose, and mechanism of action to another device that was already on the market in May 1976. The previous de-

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vice served as the *predicate* device with which the new one would be compared. This approach was justified as a way to give manufacturers the opportunity to make small improvements on the devices already on the market and to allow companies with new products to compete with very similar devices without using the more extensive PMA process. If the FDA determined that the product was reasonably safe and effective according to the 510(k) review, it was said to be *cleared for market* rather than *approved*.

Former FDA officials explain that in 1976, relatively few medical devices were permanently implanted or intended to sustain life.[3] The 510(k) process was specifically intended for devices with less need for scientific scrutiny, such as surgical gloves and hearing aids. At first, 510(k) reviews were easy for the FDA to conduct because the new devices were so similar to the devices already on the market, but the system was quickly challenged as new devices changed more dramatically and became more complex.[3] The FDA did not have the resources to develop performance standards for new moderate-risk devices or to shift more devices to the much more stringent and time-consuming PMA process.[3]

Instead, the opposite trend occurred. In an era of aggressive deregulation, the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) was passed by Congress, signed by President Bush, and interpreted by the FDA to shift the regulatory standard to "the least burdensome approach in all areas of medical device regulation."[4(p4)] Subsequently, the definition of *substantially equivalent* was modified to include products made from different materials and using a different mechanism of action if they were determined to have a similar safety profile. Since clinical trials are not required for 510(k) clearance, approval of devices would be based on biomaterials testing or other standards. Furthermore, predicate devices no longer were limited to products already on the market prior to May 1976 but could include devices cleared through the 510(k) or PMA process. In recent years, the FDA has used the 510(k) provision as the dominant mechanism for new device *clearance*, reviewing only 1% of medical devices by its more rigorous PMA process.[5] The present study was designed to examine how often the different approval or clearance processes were used for medical devices that were subsequently recalled for life-threatening problems.

METHODS

FDA CLASSES OF DEVICES AND STANDARDS OF CLEARANCE

For this study, we based our analysis on FDA assignments of medical devices to 1 of 3 classes "based on the level of control necessary to assure the safety and effectiveness of the device"[6(p1)] and on the level of risk the device poses to patients. Class I devices involve the lowest risk and include items such as tongue depressors, bandages, and crutches. Class II devices, such as electrocardiographs, contact lens solutions, hearing aids, and drills for orthopedic applications, involve intermediate risk. And Class III devices are defined by the FDA to pose the greatest potential risk and include such items as implantable pacemakers, stents, heart valves, and human immunodeficiency virus diagnostic tests. Although implants and devices that prevent impairment of health are supposed to be Class III, many hip and knee implants are designated as Class II.

Most Class I devices and some Class II devices are exempt from premarket review and most good manufacturing practices regulations.[6] Companies need not apply to the FDA for review or clearance for exempt devices but merely need to notify the FDA that they are selling the products. Class II devices considered to pose intermediate risk are reviewed through the 510(k) premarket notification process. Class III devices, which are implantable or life-sustaining devices, were intended by law to require the more rigorous PMA review process.[5]

In 2007, Congress asked the Government Accountability Office (GAO) to review the 510(k) process. The resulting 2009 GAO report described the 510(k) process as less stringent, faster, and less expensive than the PMA process and concluded that 66% of Class III submissions cleared through the 510(k) process in recent years were "implantable, life sustaining, or of significant risk,"[5(p21)] which the GAO pointed out by law should have been reviewed through the more rigorous PMA process instead.[5] The GAO noted that while the FDA had committed to stop clearing Class III devices through the 510(k) process more than 14 years earlier, the agency continued this practice.[5] In addition, the GAO reported that of the 10 670 submissions for Class II devices that the FDA cleared through the 510(k) process, "FDA's databases identified one-quarter as being for devices that were implantable; were life sustaining; or presented significant risk to the health, safety, or welfare of a patient."[5(p18)] The GAO also pointed out that these devices should have been subjected to the more stringent PMA process.

STUDY DESIGN AND MAIN OUTCOME MEASURE

Using data available on the FDA Web site (www.fda.gov), we analyzed how often the FDA issued high-risk recalls of medical devices cleared through the various FDA processes: the more rigorous PMA process, the 510(k) process, or exempt from FDA review. We started with the devices on FDA's List of Device Recalls,[7] which includes only devices about which the FDA concluded "there is a reasonable chance that they could cause serious health problems or death."[7(p1)] For each device on this high-risk recall list from 2005 through 2009, we used the FDA Web site link to product information to determine the process the FDA used to initially review or register the device.

RESULTS

From January 2005 through December 2009, the FDA included 115 names of recalled devices (involving millions of units) on their high-risk recall list. Of these 115 recalls, the FDA designated 113 as Class I recalls, which the FDA defines as the highest risk based on information provided to the FDA by health professionals, researchers, patients, or device companies. In fiscal year 2006, for example, the FDA received reports of 116 086 potential device-related injuries, 2830 potential device-related deaths, and more than 200 000 adverse event reports concerning medical devices.[8] The FDA uses these reports to help determine whether a device should be recalled because of a high risk to patients.

The PMA process was used to approve only 21 of the 113 devices listed as high-risk recalls that could cause serious health problems or death (19%).[7] Eighty were

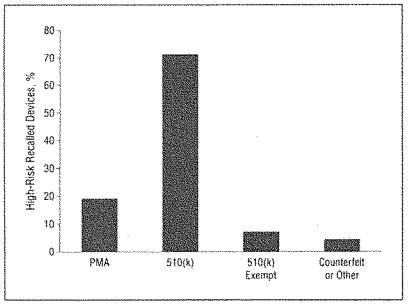

Figure 1. High-risk recalled devices classified by how the US Food and Drug Administration reviewed them from 2005 through 2009. PMA indicates premarket approval; 510(k), the less stringent premarket notification process.

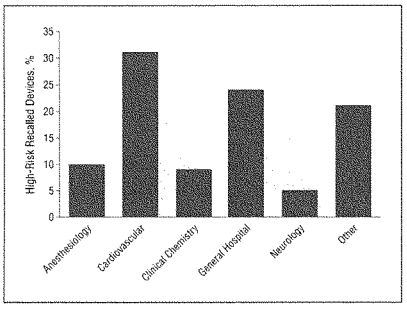

Figure 2. High-risk recalled devices categorized by medical specialty designated by the US Food and Drug Administration.

cleared through the 510(k) process (71%), and an additional 8 were completely exempt from FDA regulation and were merely registered with the FDA(7%). In addition, four were counterfeit devices or categorized as "other" (4%) and did not go through any of the 3 processes for approval, clearance, or registration (**Figure 1**).

Cardiovascular devices comprised the largest recall category, with 35 separate recalls accounting for 31% of devices on the FDA's high-risk recall list (**Figure 2**). Two-thirds of these recalled cardiovascular devices were cleared by the 510(k) process (66%; n=23), while 34% were approved through the PMA process (n=12). Despite the FDA law that requires almost all Class III devices to be approved through the more stringent PMA process, 13 of the 510(k) high-risk recalled devices were designated as Class III devices (12%). All of these recalled devices were used for treating cardiovascular disease. Most were automated external defibrillators (AEDs) approved for resuscitation of patients in cardiac arrest (**Table**). Researchers have reported that more than 20% of the almost 1 million AEDs in circulation were recalled by the FDA, and hundreds of people died due to AED malfunctions.[9]

Table. High-Risk Recalls of Class III Devices Cleared Through 510(k)

Date Recalled	Device
July 31, 2009	LIFEPAK CR Plus AED (Physio-Control Inc, Redmond, Washington)
February 12, 2009	AED Plus (ZOLL Medical Corporation, Chelmsford, Massachusetts)
February 2, 2009	Intra-aortic balloons (30, 40, and 50 mL) (Teleflex Medical, Research Triangle Park, North Carolina)
December 15, 2008	AED 10 and MRL Jumpstart AED (Welch Allyn Inc, Skaneateles Falls, New York)
August 28, 2008	LIFEPAK CR Plus AED (Physio-Control Inc)
March 17, 2008	CentriMag Extracorporeal Blood Pumping System including CentriMag Primary Console (Levitronix LLC, Waltham, Massachusetts)
October 26, 2007	AED 10 (Welch Allyn Inc)
August 24, 2007	AED 20 (Welch Allyn Inc)
February 17, 2007	Lifeline AED and ReviveR AED (Defibtech LLC, Guilford, Connecticut)
June 15, 2006	AED 20 (Welch Allyn Inc)
April 28, 2005	AED 20 (Welch Allyn Inc)
February 14, 2005	Samaritan AEDs (various models) (HeartSine Technologies Inc (Newtown, Pennsylvania)
February 3, 2005	LIFEPAK 500 AED (certain models) (Medtronic, Redmond, Washington)

Abbreviations: AED, Automated external defibrillator; 510(k), the less stringent premarket notification process.

The second largest high-risk recall category (24 % of the total) was made up of 27 general hospital devices, including insulin pumps, intravenous infusion devices, and patient lifts. Seventy-four percent of these recalled devices were cleared through 510(k) review (n=20) and only 22 % were approved through the more rigorous PMA process (n=6).

The third largest high-risk recall category (10 % of the total) was anesthesiology devices, including mechanical ventilators. All of these devices were cleared by the 510(k) process (10 devices) or were exempt from review (1 device).

The fourth and fifth largest categories of high-risk recalls were clinical chemical analysis and neurologic devices, respectively. Nine percent of all recalls were clinical chemical analysis devices such as glucose meters and other diagnostic testing equipment (n=10). These devices were cleared by the 510(k) process (7 devices, 70%), were exempt from review (1 device, 10%), or were not approved or cleared at all because they were counterfeit or in the *other* category (2 devices, 20%). Five percent of the high-risk recalls were neurologic devices (n=6), which included shunts and devices for the face, jaw, and cranium. One device was counterfeit and therefore was neither approved nor cleared; the remaining 5 of these recalled devices were cleared by the 510(k) process (83%). None was approved through the PMA process.

Only 3 devices of the high-risk recalls were in the ophthalmic category (3%). However, this category had the highest number of units recalled—57 254 133—with almost all units from the recall being 1 contact lens solution (COMPLETE MoisturePLUS multi-purpose contact lens solution; Advanced Medical Optics Inc, Santa Ana, California).[10] This lens solution was recalled when some users contracted parasitic eye infections that resulted in blindness or required a corneal transplant.

COMMENT

The present analysis demonstrates that most of the medical devices recalled by the FDA owing to serious risks during the past 5 years were approved through the 510(k) regulatory process or were completely exempt from regulatory review (78%). As such, these devices did not undergo clinical testing or premarket inspections, nor were postmarket studies required to determine safety and efficacy. While even the more rigorous PMA criteria for device approval are often scientifically inadequate to ensure patient safety,[11] PMA standards are clearly superior to 510(k) standards. Of the recalled devices cleared for market through the 510(k) process, 12% were marketed for risky or life-sustaining Class III indications, which are required by law to undergo a full PMA regulatory review. The devices recalled owing to high risks spanned a broad range of clinical applications, but cardiovascular devices represented the most common category (31%) (Figure 2). These findings demonstrate systematic problems in the implementation of existing medical device regulations that have exposed patients to serious harm.

The FDA's implementation of the 510(k) process has received considerable criticism from public health advocates and from other federal agencies in reports, medical journal articles, and testimony before Congress.[5,9,12,13] Several months after the GAO's critical report in January 2009, the FDA requested that the Institute of Medicine conduct an independent outside review (currently under way) of the 510(k) process.[14] Subsequently, in August 2010, the FDA released an internal report that suggested numerous changes intended to strengthen and clarify the 510(k) process.[15]

In that August 2010 report, the FDA 510(k) Working Group acknowledged that "in recent years, concerns have been raised within and outside of FDA about whether the current 510(k) program optimally achieves [the] goals"[15(p3)] of ensuring that devices are safe and effective and fostering innovation in the medical device industry. The FDA report suggested that clinical trials should be required in more 510(k) reviews and that safety would be enhanced if the FDA had expanded authority to require premarket inspections and postmarket studies as a condition of clearance. AdvaMed,[16,17] the largest association representing medical device manufacturers, opposes these changes.

One reason that the FDA has relied heavily on the 510(k) process is because it is less expensive and enables the relatively small Center for Devices and Radiological Health (CDRH) to review thousands of devices each year. For example, in 2005, the average cost for the FDA to review a 510(k) submission was estimated at $18 200, while a PMA submission cost the agency $870 000 to review.[5] The Congress has not appropriated sufficient funds to the CDRH to use the more expensive PMA process for most devices, and this large cost differential creates an incentive for CDRH to rely heavily on the 510(k) process. The FDA is partially supported by industry user fees, but the FDA charges much smaller user fees to review medical devices than it charges to review prescription drugs, even for the largest companies. In 2010, the FDA charged a standard fee of $4007 for a 510(k) submission (and only half that amount for small companies) and $217 787 for an original PMA (one-quarter that amount for small companies)[18] compared with $702 750 to $1 405 500 for prescription drug applications.[19] The PMA user fees provide less than one-fourth of the $870 000 average cost of the review in terms of FDA staff and resources, creating a disincentive for the FDA to select the PMA process. As part of the reauthorization of the FDA law that requires user fees, the FDA is currently holding meetings with pharmaceutical and device companies to consider changes in user fees for drugs and devices.[20,21]

In addition to not requiring clinical trials, there are 3 other aspects of the 510(k) process that are much less stringent than the PMA process: (1) under 510(k), the FDA does not generally require premarket inspections of how the devices were manufactured[5]; (2) the FDA does not require postmarket studies as a condition of clearance[22]; and (3) the FDA has much more limited authority to rescind or withdraw clearance of a 510(k) device that is found to be unsafe or ineffective.[23]

The US courts have recognized the shortcomings of the 510(k) process. In *Lohr vs Medtronic Inc*, the US Court of Appeals for the 11th Circuit in 1995 stated "The 510(k) process is focused on *equivalence*, not safety, and the question of whether a device has been deemed safe and effective cannot be resolved by looking at the 510(k) process [emphasis in the original]."[1(p1348)] In 1996, the Supreme Court affirmed the 11th Circuit conclusions that "[s]ince the § 510(k) process is focused on *equivalence*, not safety, substantial equivalence determinations provide little protection to the public [emphasis in the original]."[24(p493)]

In an analysis funded by AdvaMed, a Batelle report recently concluded that the 510(k) process was adequate because the number of high-risk recalls represents a small proportion of devices cleared through the 510(k) process.[25] However, that analysis did not take into account the public health implications for patients and the US medical system. As noted herein, FDA data and previous studies in medical journals indicate that high-risk recalled 510(k) devices were used by tens of millions of patients, exposing them to potential harm and adding substantial costs to medical care. On a policy level, the present analysis and the 2009 GAO analysis[5] indicate that the FDA is not fully implementing the law that requires high-risk medical devices to be approved through the PMA process and frequently uses the 510(k) process instead.

An important question is whether the risks resulting from subsequently recalled devices could have been prevented if the 510(k) or exempt devices had been subject to a more rigorous review process. Clinical trials and other more rigorous premarket data collection required in the PMA process but not the 510(k) process could uncover design flaws or manufacturing flaws before a device is sold. Premarket inspections, which are required for PMA devices but rarely used as part of the current 510(k) review process, could also uncover manufacturing flaws that result in products that are less safe or less effective for patients and consumers. Requiring postmarket studies as a condition of approval, which is an option for PMA approval but not usually for 510(k) clearance, could help determine risks sooner than the current adverse-event reporting system.

CONCLUSION

Medical devices cleared through the less rigorous 510(k) pathway comprise more than two-thirds of the products that are recalled by the FDA because they could seriously harm patients or result in death. When devices that were intentionally exempt from any FDA review were added to the 510(k) devices, they comprise more than 3 out of 4 of the high-risk recalls during the last 5 years. Thus, the standards used to determine whether a medical device is a high-risk or life-sustaining product prior to approval are clearly very different from the standards used to recall a medical device as life threatening. Our findings reveal critical flaws in the current FDA device review system and its implementation that will require either congressional action or major changes in regulatory policy.

The results of the present analysis indicate that the number of high-risk recalls of medical devices and the number of patients affected by these recalls would be substantially decreased if the following changes were made in the FDA process:

1. The FDA fully implements current law that subjects "life-saving and life sustaining" (Class III) devices to the PMA process;
2. The FDA's definition of a high-risk device takes into account the potential risks if the device fails;
3. The FDA expands the use of their authority to inspect the manufacturing of 510(k) devices just as they do for devices approved through the PMA process; and
4. The FDA strengthens their authority to use special controls for 510(k) devices as they do for PMA devices, such as postmarket surveillance, performance standards, and product-specific and general guidance documents.

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REFERENCES

1. Lohr v Medtronic Inc, 56 F3d 1335 (11th Cir 1995). http://scholar.google.com/scholar_case?case=9155174046926497575&q=Lohr+v.+Medtronic,+Inc.+&hl=en&as_sdt=2,9. Accessed January 13, 2011.
2. US Food and Drug Administration. Medical devices premarket approval (PMA). http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm. Accessed November 9, 2010.
3. Public health effectiveness of the FDA 510(k) clearance process: balancing patient safety and innovation: workshop report (2010) http://www.nap.edu/openbook.php?record_id=12960&page=9. Accessed November 30, 2010.
4. US Food and Drug Administration. interactive review for medical device submissions: 510(k)s, original PMAs, PMA supplements, original BLAs, and BLA supplements. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm. Accessed January 13, 2011.
5. US Government Accountability Office. FDA should take steps to ensure that high-risk device types are approved through the most stringent premarket review process: GAO-09-190: January 2009. http://gao.gov/new.items/d09190.pdf. Accessed November 9, 2010.
6. US Food and Drug Administration. Device classification. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm. Accessed July 24, 2009.
7. US Food and Drug Administration. Medical devices: list of device recalls. http://www.fda.gov/MedicalDevices/Safety/RecallsCorrectionsRemovals/ListofRecalls/default.htm. Accessed August 17, 2010.
8. US Food and Drug Administration, Center for Devices and Radiological Health. CDRH FY 2006 highlights. www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm129258.pdf. Accessed August 21, 2009.
9. Maisel WH. Medical devices: are current regulations doing enough for patients? testimony before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives: June 2009. http://energycommerce.house.gov/index.php?option=com_content&view=article&id=1677. Accessed August 31, 2009.
10. US Food and Drug Administration. Medical & radiation emitting device recalls. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=52779. Accessed March 2, 2010.
11. Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. *JAMA*. 2009;302(24):2679-2685.
12. Zuckerman D. Testimony on reauthorization of the Medical Device User Fee and Modernization Act before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives: May 2007. http://archives.energycommerce.house.gov/cmte_mtgs/110-he-hrg.051607.Zuckerman-Testimony.pdf. Accessed November 9, 2010.
13. Redberg RF. Medical devices and the FDA approval process: balancing safety and innovation; comment on "prevalence of fracture and fragment embolization of bard retrievable vena cava filters and clinical implications including cardiac perforation and tamponade." *Arch Intern Med*. 2010;170(20):1831-1833.
14. US Food and Drug Administration. Public health effectiveness of the FDA 510(k) clearance process: balancing patient safety and innovation: workshop report, October 14, 2010. http://www.books.nap.edu/openbook.php?record_id=12960&page=1. Accessed January 13, 2011.
15. US Food and Drug Administration. CDRH preliminary internal evaluations—volume I: 510(k) working group, preliminary report and recommendations. August 2010. http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220784.pdf. Accessed August 17, 2010.
16. AdvaMed. AdvaMed statement on FDA public meeting (press release). October 2010. http://www.advamed.org/MemberPortal/About/NewsRoom/NewsReleases/PR-FDA510K-10810.htr. Accessed November 9, 2010.

17. Medical Device Industry Applauds Lawmaker Concern Over Review Process. *CQ Healthbeat News*. October 13, 2010.
18. Federal Register. Medical device user fee rates for fiscal year 2010: Docket No. FDA-2009-N-0338: August 2009. http://edocket.access.gpo.gov/2009/E9-18456.htm. Accessed June 21, 2010.
19. Federal Register. Prescription drug user fee rates for fiscal year 2010: Docket No. FDA-2009-N-0339: August 2009. http://edocket.access.gpo.gov/2009/E9-18457.htm. Accessed June 18, 2010.
20. Federal Register. Prescription Drug User Fee Act; public meeting: docket No. FDA-2010-N00128: March 2010. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2010_register&docid=fr16mr10-68.pdf. Accessed August 18, 2010.
21. Federal Register. Medical Device User Fee Act; public meeting: Docket No. FDA-2010-N00389: August 2010. http://edocket.access.gpo.gov/2010/2010-19843.htm. Accessed August 13, 2010.
22. Rosecrans HS. FDA's 510(k) workshop: issues related to postmarket surveillance and new information about marketed devices: February 2010. http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM201345.pdf. Accessed March 2, 2010.
23. Tillman D-B. Understanding the premarket notification 510(k) process: FDA's 510(k) working group presentation to the Institute of Medicine: March 2010. http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/510kProcess/2010-MAR-01/Tillman-The%2510k%20Working%20Group.ashx. Accessed November 9, 2010.
24. Medtronic Inc v Lohr, 518 US 470 (1996). http://scholar.google.com/scholar_case?case=9764091134585266905&q=Medtronic,+Inc.+v+Lohr+et+vir&hl=en&as_sdt=2,9. Accessed January 13, 2011.
25. McCarty M. Batelle says 510(k) recalls since '98 are at less than 1%. http://www.medicaldevicedaily.com/servlet/com.accumedia.web.Dispatcher?next=bioWorldHeadlines_article&forceid=72862. Accessed November 9, 2010.

INVITED COMMENTARY

ONLINE FIRST

Medical Device Recalls

Get It Right the First Time

Consumers are justifiably upset when their cars, toasters, and baby food bottles are recalled. Recalls make us all question the safety of the products we take for granted. But what about the products permanently implanted inside our bodies? Surely they have been sufficiently tested to ensure that no one will need to bring their thorax to the shop for removal and replacement. It is sad and troubling to learn that we cannot count on this assurance for some medical devices.

Medical devices are divided into 3 classes by the FDA, according to their level of risk to patients.[1] Class I devices pose a low risk, present minimal potential harm to patients (items such as stethoscopes and bandages), and are subject to minimal regulation. Class II devices pose a moderate risk, include such items as hearing aids and wheelchairs, and may be cleared through the 510(k) premarket notification process, whereby they can be marketed if they are substantially equivalent to a predicate device. Importantly, clinical trials are not necessary for these 2 device classes.

Class III devices, such as stents and implantable cardioverter-defibrillators, pose a potential high risk and are defined as those devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[1] The FDA states that "Premarket approval (PMA) is the *required* process of scientific review to ensure the safety and effectiveness"[1] of these devices

A 2009 GAO report of all FDA reviews of high-risk devices in fiscal years 2003 through 2007[2] found that more high-risk devices get cleared via the 510(k) than through the original PMA process. Simply put, this means that more often than not, the highest-risk devices are being approved, marketed, and used in patients without any clinical trial data. Therefore, although the FDA committed some time ago to require that high-risk devices be either evaluated through PMA or reclassified to a lower risk class, neither has yet occurred. Indeed, it has been over 20 years since Congress passed the Safe Medical Devices Act, envisioning that this would happen.[2] However, currently, only 1% of all devices go through PMA.

Zuckerman and colleagues demonstrate the dangers to patient safety posed by these innumerable device misclassifications. They review the approval pathway for all high-risk recalls of medical devices from 2005 through 2009. Although high-risk device recalls are defined as those that could cause serious health problems or death, more than three-fourths of these potentially lethal devices were not approved by PMA. Instead, most were cleared through the weaker 510(k) process, which does not require any clinical data on safety or effectiveness before or after approval. A few were even considered exempt from review. Ultimately, this means that devices not considered during the approval process to pose a potentially high risk might still be subject to a high-risk recall. This paradox presents a critical safety concern.

Cardiovascular devices were the most common category for high-risk recalls. For example, hundreds of deaths have been attributed to AED malfunctions, while it remains unclear how many lives these devices may have saved. Another worrisome example is the Sprint Fidelis (Medtronic, Minneapolis, Minnesota), an implantable cardioverter-defibrillator approved by the FDA in 2004 without any premarket clinical testing.[3] It was subsequently implanted in 268 000 patients over 3 years before being voluntarily withdrawn by the manufacturer owing to the possibility of lead fracture, which led to inappropriate shocks or loss of function. Regrettably, by early 2009, the manufacturer had already identified 13 patient deaths related to the defective leads.[4]

Undoubtedly, some recalls are unavoidable as our knowledge and experience with a device grows. However, we must make sure that before devices are approved and widely disseminated, we have done due diligence to determine that they are safe and effective. For

Mr. PITTS. The chair thanks the gentleman and recognizes Mr. Hall for 5 minutes.

STATEMENT OF RALPH HALL

Mr. HALL. Chairman Pitts, Ranking Member Pallone, members of the committee, I appreciate the opportunity to appear today and to discuss with you the 501(k) system in general and specifically some research I have done into the safety profile of devices cleared via that process.

I serve on the faculty at the University of Minnesota Law School where I teach in the food and drug law area and concentrate my writing and my research in that area. In addition, I work part time with the law firm of Baker & Daniels, counseling firms in FDA matters; and with three other individuals we have formed a start-up medical device company called MR3 Medical.

Going back several years when the debate over the 501(k) system began, I observed that the debate was taking place with little data. There was a lot of anecdote, a lot of individual events that people were discussing; and at a public meeting about a year ago I commented we were involved in a ready, fire, aim situation.

And, therefore, I conducted a study—the first of its kind I believe—to try do assess the safety profile of 501(k) products. This was funded by the Kauffmann Foundation out of Kansas City. I was given total academic freedom.

It should be clear that I am speaking in my individual capacity, not on behalf of any entity, particularly the University of Minnesota. In this study, we analyzed Class I or high-risk recalls for over a 5-year time period. We coded these for a number of factors, including the reason for the recall. We think that is critical, because you need to identify events, recalls, then the cause of that, in order to identify what can be done to address it.

The results of this is we had 118 Class I recalls, 112 of which were relevant. The other 6 involved counterfeit products, things like that. Of these, 89 involved 501(k) products. This has to take into account the number of 501(k) submissions during the time frame. You can't simply look at the numerator. During this same time frame, the best estimates are, there were over 19,000 501(k) submissions. What that means is, from a safety perspective, greater than 99.5 percent of all 501(k) submissions did not result in a Class I recall during the study period.

We then further delved into the data and identified which reasons for the recall related to post-market issues, as compared to pre-market issues. Obviously, an issue that happens 5 years after the product is approved or cleared, because of a labeling mistake or whatever, is not accountable to the approval process. And it turns out that less than half of all recalls relate to issues that could have involved pre-market activities. We further analyzed the data, looking at the reasons for the recall, and less than 9 percent of all recalls involved issues other than quality system issues.

What this indicates to us is the system, as a whole, from a safety perspective, is operating very well. Can we do better? Of course. Do we need to do better? Of course.

To help with that effort, then, we did a subanalysis even further by type of device, and we identified the concentration of recalls in

automatic external defibrillators and infusion pumps—28 percent of all recalls. Interestingly, the agency has now commenced two initiatives on those products. From our perspective, that is the right way to approach this: identify the issue and address the specific issues. The information I am talking about has been presented to the IOM, reviewed with FDA and other stakeholders.

So what does our study then conclude? FDA has an excellent safety record in the 501(k) program. Improvements can be made. We need to strive for improvements. We need to always concentrate on the risk-benefit analysis. And the most effective way to improve the safety profile of products is to increase and further emphasis on quality systems, as compared to pre-market products.

Stated differently, change in the pre-market clearance process, based upon our data, will have a minimal effect on reducing the number of recalls. Therefore, our conclusion is that the focus should be on quality systems as a primary way to improve the safety of products for the U.S. public.

Thank you very much. I would be happy to answer any questions.

[The prepared statement of Mr. Hall follows:]

Summary of Testimony

Ralph F. Hall, Distinguished Professor and Practitioner
University of Minnesota Law School
U.S. House of Representatives Energy and Commerce Subcommittee on Health
Hearing on "Impact of Medical Device Regulation on Jobs and Patients."
February 17, 2011

I conducted a detailed study of the safety profile of medical devices from 2005-2009 by evaluating Class I (or high risk) recalls[1] of all medical devices approved through the PMA system, cleared through the 510(k) process, or otherwise exempt.

This study found that, 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 recall. More relevant, over 99.7% of 510(k) submissions did not result in a Class I recall for any reason relevant to the 510(k) premarket clearance system.

Less than 9% of Class I recalls involve possible undiscovered clinical risks. As such, increased preapproval clinical testing would not have any meaningful impact on number on Class I recalls.

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. Over 90% of all Class I recalls (including both premarket and post market issues) are directly related to quality system issues (so-called QSR systems). Improved QSR systems will have the greatest effect in reducing the number of Class I recalls.

The study did identify a bolus of Class I recalls in two device types – automatic external defibrillators (AEDs) and infusion pumps. Any changes to the 510(k) process should be targeted to demonstrated problems rather than applied broadly.

This study did not address patient access issues, innovation or economic issues.

[1] FDA categorizes all recalls into one of three classes, according to the level of hazard involved. Class I recalls are assigned for "dangerous or defective products that predictably could cause serious health problems or death." The recall class is separate from and not relevant to the product's classification for premarket review processes.

Written Statement

Ralph F. Hall

Distinguished Professor and Practitioner

University of Minnesota Law School

U.S. House of Representatives Energy and Commerce Subcommittee on Health

Hearing on "Impact of Medical Device Regulation on Jobs and Patients."

February 17, 2011

Good morning, 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. 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 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]

Summary:

The study I focus my comments on assessed the overall safety profile of medical devices approved or cleared by FDA from 2005-2009 by using Class I safety recall data. This study[2] 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 recall. More relevant to this hearing, 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. 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.

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[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] This research 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.

3. 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.
4. 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 systems). Improved QSR systems will have the greatest effect in reducing the number of Class I recalls.
5. 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 510(k) process should be targeted to demonstrated problems rather than applied in some random, shotgun way.
6. 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 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 didn't 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 not to be aware of this. Second, some stakeholders were advocating making major changes in the 510(k)

system to address presumed safety problems. I was then particularly struck by the fact that there was not 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 were simply looking 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 data bases, 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).

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 grouping 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:

- First, we relied entirely upon publicly available data. We assume that the information in the FDA data bases 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.
- 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.
- 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 recall.
- 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.

- 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 10 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 data bases 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.

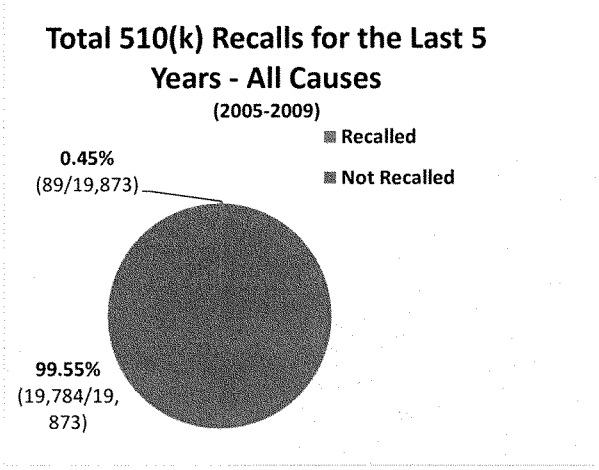
	Total Recalls	Recalls for Pre-Market Issues	Recalled for Post-Market Issues	Recalled for Other Issues	Percent of Recalls to Total Recalls
Class I or u/k	7	1 (14.2%)	6 (85.7%)	0 (0%)	5.9%
510(k)	95	43 (45.3%)	46 (48.4%)	6 (6.3%)	80.5%
PMA	16	7 (43.8%)	9 (56.3%)	0 (0%)	13.56%
TOTAL	118	51	61	6	118

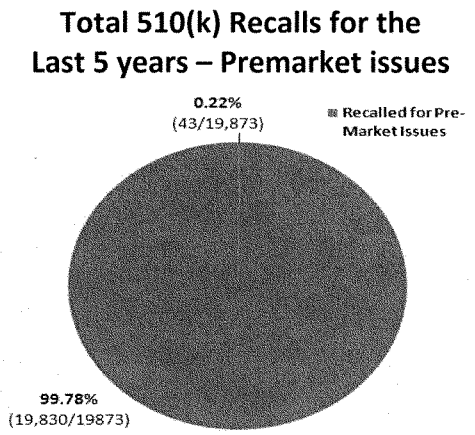
As seen below, a very small percentage of 510(k) submissions led to a Class I recall during our study period. The first chart shows the ratio of 510(k) submissions to all Class I recalls and the second chart shows the ratio of 510(k) submissions to Class I recalls related to any theoretical premarket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

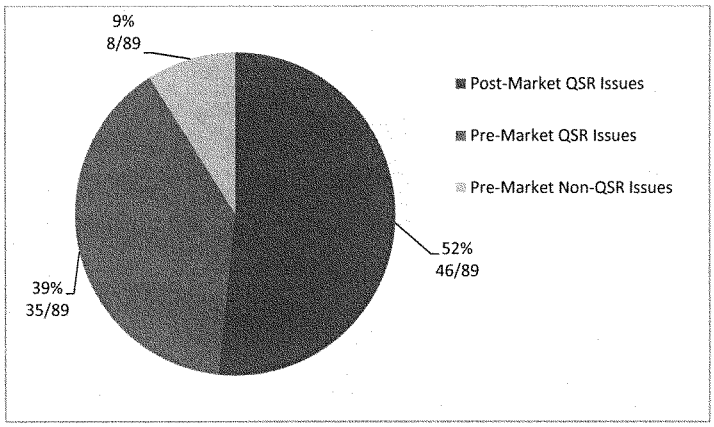




Total 510(k) Submissions in 10 years	39,747
Average Submissions in 5 year time period	19,873
Total 510(k) Recalls for 2005-2009	89
Total 510(k) Recalls for Pre-Market Issues for 2005-2009	43

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.

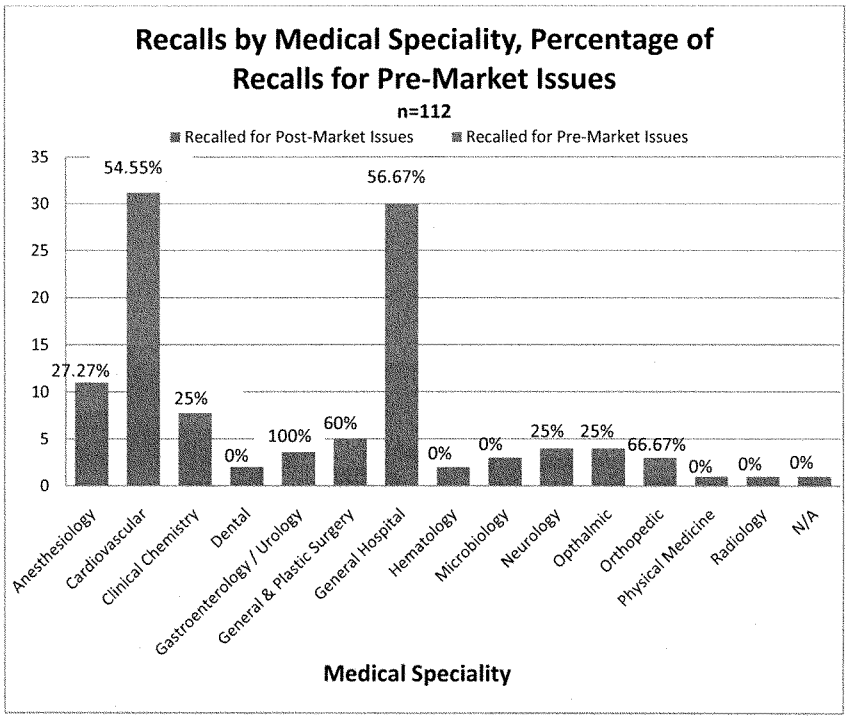
This conclusion is reinforced when we reviewed the role of quality systems in recalls. As shown below, over 90% of all Class I safety recalls are related to quality system issues and not to other factors such as a lack of clinical trials.



Clearly, this data demonstrates that all stakeholders should concentrate on QSR issues -- not the 510(k) system in its entirety -- as the most effective way to provide greater patient safety.

Making the 510(k) system more burdensome will have a negative impact on patient access to new technology without any corresponding patient benefit.

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 9 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 third parties finding very similar numbers and reasons for Class I recalls.

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.

Thank you for your time and attention. I would be happy to answer any questions you might have.

Mr. PITTS. The chair thanks the gentleman, thanks all the witnesses for your testimony.

And we will go to questions at this time. The chair recognizes himself for 5 minutes for questioning.

We have heard a lot of discussion today on the medical device approval process used by the FDA. Mr. Hall, your study focused on recalls of medical devices approved through the 501(k) and the PMA process. Based on your research into the recalls, is FDA clearing unsafe products?

Mr. HALL. In my study, FDA has an excellent record in approval of products, with greater than 99.5 percent of products not experiencing a recall.

Mr. PITTS. Could you comment, please, on the study published this week in the Archives of Internal Medicine? How did those study authors end up with recall results that are much higher than what your study found? And can you comment on the methodology used in the Archives of Internal Medicine study?

Mr. HALL. Yes, Mr. Chairman. The data that was used by both studies ended up with very similar numbers for what I call the numerator. I had 118 Class I recalls. I believe they had 112 or 113, something like that.

Where the differences are is that we also went beyond just looking at the number of absolute recalls, but looked at the percentage of that compared to the number of submissions. If my daughter comes home and got, you know, 80 wrong out of 150, which is the number of PMAs, that is a problem. But in the 501(k) world, there are over 19,000. So we are talking about in their study 80, in my study 89 recalls out of over 19,000.

We also looked at the reason for the recall. That is critical to understand what to focus on.

Next, there is a confusion about comparing high-risk devices for approval process to high-risk devices for recall. Those are very different things, and it is important that the committee understand that. The classification for an approval is the risk for the intended use. The recall is the risk to the patient for the malfunction.

And let me give you a very simple example, a tongue depressor. No one would consider a tongue depressor to be high-risk or needs a clinical study. But if the tongue depressor gets contaminated with a deadly bacteria, the recall for that tongue depressor should be a high-risk recall. And so, you cannot link the approval classification with the recall.

A final comment on the lawyer—I am a law school professor. At a different environment, we should talk about—there are a number of statements about the law in the article, which I think need to be corrected.

Mr. PITTS. Thank you.

Dr. Makower, in your work, you find that companies spend $31 million to bring low-risk devices to market. And, of that amount, $24 million is spent navigating the FDA approval process. Your findings for bringing higher-risk devices to market are even more staggering. Companies must spend $94 million, spending $75 million navigating the FDA approval process.

Can you break down the investments that a typical company might make to help them navigate the FDA? How feasible is it for

a small company to come up with appropriate funding to navigate the process at the FDA?

Dr. MAKOWER. Quite honestly, these are figures that are exceeding venture capital's ability to fund startups to these levels. And, thus, that is why we are seeing a decrease in the number of startups, because people don't want to take that big financial risk for getting these products all the way to market. And with those costs increasing, that capital just is not available.

Mr. PITTS. Mr. Deem, would you care to comment on that, too? Have any of your companies closed because of the expense involved in navigating the FDA process?

Mr. DEEM. Each of the three examples that I gave today, at the end of the day, ended up shutting the doors because it was the judgment of the board of directors that further investment to continue through the regulatory process, given the barriers that they had already hit and the moving milestones that they were being asked to hit, the further investment was just not justified.

So it wasn't that we didn't think that ultimately we could get through the process. We thought perhaps eventually we could get through. But given the moving goalposts involved, the extra investment was not justified, and the companies were shut down.

Mr. PITTS. Just one final question, Dr. Makower. According to your work, device approval times in the U.S. are much longer in the U.S., compared in Europe. And you find that those companies who spoke with the FDA about conducting a clinical study for their low- to moderate-risk device before making a regulatory submission, the pre-market process took an average of 31 months from first communication to being cleared to market the device. In contrast, the equivalent process in Europe took an average of 7 months.

And the higher-risk devices seeking pre-market approval, companies indicated, took an average of 54 months to work with FDA from first communications to being approved to market the device. In Europe, it was 11 months.

Did your study identify any reasons as to why there is such a discrepancy in approval times?

Dr. MAKOWER. The major difference is that, in Europe, a study run by high-quality investigators that makes clinical sense to a specialist in the field are generally accepted as data for approval, and there isn't a lengthy negotiation over end points or study design that usually happens in the United States.

Whereas, in the United States, that process, even just the process of obtaining an IDE, which is the approval necessary to do a study in the United States, that can take years. And so that, alone, is a reason why the two systems are different.

Mr. PITTS. Thank you.

The chair recognizes the ranking member for 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I am going to ask Dr. Shuren a question. But before I do, I just wanted to say, I think it is important that when we talk about innovation, which is what I talked about in my opening, and, of course, the President talks about it constantly, that when we talk about innovation, we talk about safety and effectiveness of devices

at the same time. Because innovation in devices can generate positive changes in the health of all Americans but only if we can properly ensure the safety of those devices.

But navigating the FDA process, you know, shouldn't be unpredictable and it shouldn't be unreasonably long. So I was a little stunned to hear Dr. Makower's finding that it is 2 years longer for approval in the U.S. As compared to Europe for low- or moderate-risk devices and 3½ years longer for higher-risk devices.

I wanted to ask Dr. Shuren, you run the center responsible for these approval times. And I find these numbers outrageous, this difference between the U.S. and Europe. How is that possible? What is the situation?

Dr. SHUREN. I don't think, with all due respect to Josh, I don't think the study is an accurate reflection of what is going on now. And putting aside the very low reporting in this survey, which means it is going to be biased to the most dissatisfied, if you actually look at the data on PMAs and this long time between us for approval and the EU, the time frame is at 54 months versus 11 months.

In the U.S., you can come talk to us before you have designed a clinical trial. You can talk to us about what the data needs are, then develop the clinical trial. Regardless, you are going to come in at the time you are going to do a clinical trial.

If you applied that here for the EU, look at the 11 months. It means you would come in to talk, you would develop a clinical protocol, you would set up your study, you would enroll your patients, you conduct the study, you collect your data, you analyze it, you put together a submission, you send it to the private company who reviews it, and they make a decision. In 11 months? That means a clinical study of 4 weeks?

This is comparing apples and oranges. This is comparing when you come in to talk to us as opposed to review times. If you actually go ahead——

Mr. PALLONE. I am going to have to interrupt because I have to get my other questions in here.

I was heartened to hear President Obama's comments at the State of the Union Address about how the U.S. needs to win the future and promote innovation. I keep talking about it. In my own State, you know, we have a serious life science industry. And I know that FDA also places a high importance on promoting innovation.

But you mentioned something in your testimony about the steps you have implemented to promote innovation. Can you tell us about that, what you are exactly doing to promote innovation?

Dr. SHUREN. Certainly. Well, starting with even the actions we are talking under our 501(k) improvement plan, it is about increasing predictability, consistency, and transparency through guidance, through training, through administrative changes to make sure there is greater management oversight in decision-making, even leveraging experts outside of the agency to better inform us on tough scientific questions.

But we are also announcing an innovation initiative, creating what we call an Innovation Pathway. It is a paradigm shift in how we approach breakthrough technologies, in which we forward-push

our resources. We frontload them so we are involved early on, and we can address some of these tough scientific questions early on. And we think, under that program, we can cut our review time in half.

Mr. PALLONE. Thank you.

Let me just ask you one more thing. I want to ask about resources, Dr. Shuren. As I am sure you are aware, the House Republicans have put forward a continuing resolution that would slash the FDA's budget by 10 percent. And these are cuts on top of what is already an underfunded agency, in my opinion.

If these drafted cuts were to be passed into law, will you have the resources to support new initiatives like this Innovation Pathway? And how would these cuts affect your ability to make clearances and approvals more timely and practicable?

Dr. SHUREN. Well, the Innovation Pathway would be a non-option. And for the rest of what we do, this would result in increased delays in decisions. It would deny patients truly safe and effective innovative technologies. And it will result in jobs being lost.

Mr. PALLONE. Well, I am just going to go down the panel. Let me just ask—and I have a minute left—does anyone on this panel think that drastic cuts to FDA make much sense right now?

We will start—obviously, Dr. Shuren doesn't.

Dr. Makower?

Dr. MAKOWER. Drastic cuts to—sorry?

Mr. PALLONE. Well, you could say "yes" or "no" if you want. Do you think that drastic cuts, the cuts we are talking about, make sense now?

Dr. MAKOWER. I am not sure.

Mr. PALLONE. All right.

Mr. Deem?

Mr. DEEM. I haven't looked closely at the situation. Obviously, I would need to look at the efficiencies that are involved in the process, as well as the overall number.

Mr. PALLONE. Okay.

Dr. Redberg?

Dr. REDBERG. I think substantial investment is required for the FDA for resources and staffing, as well as the entire electronic infrastructure so that it can actually do pre-marketing and post-marketing surveillance, as it would like to.

Mr. PALLONE. Thank you.

Dr. Nissen, yes or no?

Dr. NISSEN. No.

Mr. PALLONE. Mr. Hall?

Mr. HALL. My thinking, if that is what the Congress decides, the agency is capable of meeting its statutory and public health requirements.

Mr. PALLONE. Okay. Thank you, gentlemen.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and yields to Dr. Burgess for 5 minutes for questions.

Dr. BURGESS. Thank you, Mr. Chairman.

And, of course, funding for the FDA, just to pick up on Mr. Pallone's point, has been an issue that this committee has looked at. For the 6 years that I have been on the committee prior to this

term, we have increased the authorization for FDA spending on multiple occasions, but with both Republican and Democratic appropriators, those funding levels have not been met.

So it is all well and good to criticize a process that is going on today. It is a process that was left over from last year. It is unfortunate it looks the way it does, but I really appreciate Mr. Hall's comments. It is up to us to provide the funding. It is up to the administrator at the FDA to get the job done with the tools at hand.

Why would you pay more for what you are getting? We want more of this? How far away from desirable do we care to be? And this was really what is driving a lot of this discussion today.

It appears that the average 501(k) decision has risen almost 20 percent from 2002 to 2008: 97 days in 2002, 116 days in 2008. The director recently released a letter emphasizing, just as you reiterated this morning, the FDA's dedication to increasing predictability, reliability, efficiency, and transparency of the regulatory pathways—all good things.

Last year, when I was on another subcommittee, I wrote to you with my concerns that you were, in fact, altering the processes, but doing so independently, without consulting Congress. So I will reiterate the question I asked you in a letter last summer. How, specifically, does the FDA plan to do this? And why did you undertake those efforts with the IOM study still not completed?

Dr. SHUREN. So what we plan to do is a series of actions that we announced. And when we put together these reports—and we undertook these reports in part because of concerns that were raised by industry and also concerns that were raised by consumer and patient groups. And we went out and we conducted comprehensive outreach. We had two public meetings, three public dockets, three town hall meetings. We put out two reports, 55 recommendations in the summer, and we asked for public comment on that. We came and we briefed staff on the Hill, both before and after we went out with our actions just a few weeks ago.

Those 25 actions are based around greater clarity through guidance about the 501(k) program, about when to submit clinical data, about fixing what is called the de novo process—it is a process for the lower-risk innovative devices—because it has been broken for years, and it needs to be fixed; better training for my staff. I rolled in—we did not have core competencies. We are now putting in place core competency training——

Dr. BURGESS. Let me stop you there. And perhaps we can get some of this accomplished in a written exchange that I had asked for last summer.

Dr. Redberg emphasized the lack of effective electronic capability of handling the data, the infrastructure, the architecture for the information technology. How are you doing with that? You have been given additional funds over the last 3 years. Are you there yet? Are you getting there? Have you been able to digitize your data, not just in the new drug application, not just the device application, but throughout the agency?

Dr. SHUREN. I can't speak for throughout the agency, but we are moving forward. We have made progress for setting up the new database for adverse event report reporting——

Dr. BURGESS. But we kind of hear that every year. And are you there yet?

Dr. SHUREN. We are not there yet.

Dr. BURGESS. And give us a reasonable expectation of when that might happen.

Dr. SHUREN. We are expecting to have the first prototype up this year.

We will also be coming out this year with the unique device identification regulation, too. And that is going to be critical for linking a device with the clinical experience with that device we don't have right now.

Dr. BURGESS. An excellent idea and, I think, one we have heard before. It is just that we are all anxious for that to happen. Because, as I indicated in my opening statement, there are going to be real challenges for the researchers at NIH, Don Berwick and his crew at CMS being able to implement those new tools that they are given by NIH, and you guys stand in the middle. So you are either going to be the facilitator or the bottleneck. And I just pray that you are going to take that facilitator role very, very seriously.

Let me just ask you one other question that came up about—I think it was Mr. Deem, or perhaps it was Dr. Makower that brought it up—the Newsweek article on the race to grow new organs, and organs being grown on scaffolding with the patient's own cells.

There was a doctor, Anthony Atala, at North Carolina growing new body parts for a particular type of difficulty that children could be born with. And, as a consequence, he received, I guess, an emergency designation to do this in seven, eight, or nine patients from the FDA. Showed some great results. Of course, no rejection because it was the patient's own cells. Vascularization occurred after these devices were implanted. And when you got back to him, you said, "Well, we will have to show it works in animals." I mean, this is kind of crazy stuff that just drives people nuts.

You have a small series of 7 to 10 patients where it is working, and you tell this guy, "Go back to square one, spend another $5 million, and let's prove this will work in dogs before we do it in any more people." That is why it goes to Europe. That is why it goes to Europe.

Dr. SHUREN. We will look at it, but this may actually involve the other center, the Center for Biologics.

But we do take it very seriously. And I will tell you—I am new at the helm, a little bit over a year. And I will tell you, during that time, we have been making some important changes. And our performance—and you did ask before—our performance actually has been improving. And that 501(k) time actually, for us, we have been doing very well.

What we have found, though, is that the times are going up because industry isn't pulling its fair share. It has been sending us poor-quality submissions. We have been seeing poor clinical studies. And we meet with companies, and they like to meet with us, and they are ignoring our recommendations in terms of what to do.

If we are going to fix this, FDA needs to make changes. And we made a commitment to do that, and we are moving forward on

them. But we also need industry to be held responsible, too, for its failures, for the things that we cannot control.

Dr. BURGESS. Mr. Chairman, could I just ask unanimous consent that industry be allowed to respond? Dr. Makower and Mr. Deem are sitting right there.

Mr. PITTS. Without objection, so ordered.

Dr. MAKOWER. I think the issue is, what is reasonable? And that is what this comes down to. And I think you pointed out an example of exactly the type of thing that frustrates industry.

We are trying to help patients and we are trying to bring therapy forward, and sometimes the requests and the requirements—the reason why we can't get agreement on a clinical trial protocol is because what is being asked may sometimes be extraordinary, beyond what is a reasonable requirement, and sometimes what is impossible, where you know you have an early-stage technology, it must evolve.

And so, we are depriving physicians, patients the opportunity to get access to these things earlier. And that is the net impact, is that disagreement, that time frame is what is really delaying innovation reaching patients.

Mr. PITTS. The chair thanks the gentleman, and recognizes the gentleman from Illinois, Mr. Shimkus, for 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman.

Mr. Chairman, if you don't keep a hold on Burgess, he will just consume the whole time. I learned that as ranking member last Congress. He is very impassioned, and we appreciate his commitment.

Let's just talk. The Nation sent a new Congress here to deal with the national debt, the deficit, and job creation. The hearings that we have had here in the committee are really focusing on, how do we create jobs without spending money? And the answer is, we have to ease the regulatory burdens.

The agency is not going to get any more money. So you can ask all you want; there is no more money. So if you have demands of which you have to do, you have to talk to us and say, "You know, you put this demand on us"—which we have. Part of it is our problem. Say, "This is really a stupid thing we shouldn't be doing." And if we jettison this, that will free up money to do what we really need to do.

So, you know, I reject this argument that you all need more money. Just like people at home, just like businesses who are in lean times, they have to make difficult decisions to get back to core competencies. And I think there is an argument, especially in this, that we are slowing the process down so much in some of these devices it is nonsensical, and it hurts job creation.

Now, I have a couple of questions that I want to talk about. In October, at that time, I was ranking member of this subcommittee. I joined 11 of my colleagues in sending a letter to FDA on the 501(k) reform changes. In that letter, we asked FDA for an economic analysis of those changes so we could know if it would hurt American job creation.

Dr. Shuren, if you can give me a "yes" or "no" answer, did you provide that economic analysis?

Dr. SHUREN. No.

Mr. SHIMKUS. Thank you. That is typical of Federal agencies that I have been dealing with for the last couple of weeks.

Mr. Makower and Mr. Deem, since the FDA didn't provide it, let me ask you, what could be the economic impact of these changes on American device companies?

Dr. MAKOWER. These changes being?

Mr. SHIMKUS. The 501(k)——

Dr. MAKOWER. Many of them are things that make sense and, actually, I don't really think even need much approval. However, there are several changes that are being proposed that could have a devastating impact on our ability to bring——

Mr. SHIMKUS. Quickly, give me a couple examples.

Dr. MAKOWER. One example is, kind of, the definition of what is an intended use. And depending on how that is characterized, if that is characterized in one way versus another, it may require companies to study not only the intended use that they are actually pursuing to get a label on, but all other possible indications that doctors might use it on, which would delay access and would probably prevent many technologies from reaching the market.

Mr. SHIMKUS. Mr. Deem, can I ask you? Did you follow the question, and do you have a response?

Mr. DEEM. Sure. I think we are also concerned and watching closely what is going to happen with the designation of a Class II-b and the requirements and guidances for clinical study that will come out of that. And that is still yet to be determined, but we are watching it very closely.

And the reason we are watching it very closely is that the FDA right now has the latitude to require clinical data from a 501(k). In fact, the only two 501(k)s that we have done out of our 14 companies, we have provided clinical data. We have provided randomized, controlled, blinded clinical data for 501(k)s.

So it is a misnomer that that doesn't happen. It certainly does, and it can, under the current system. What we worry about is how rigorously and how rigidly these other designations might codify that.

Mr. SHIMKUS. Thank you.

And I am going to try to get this done in my last minute.

Dr. Shuren, I understand that you are sending seven of the most important 501(k) changes to a panel of the Institute of Medicine. I understand, also, there are serious questions as to the composition of this panel and the role you gave this panel. So I have the following questions.

Does this panel have any innovators or inventors?

Dr. SHUREN. I do not believe so.

Mr. SHIMKUS. Does this panel have any biomedical engineers or technical experts?

Dr. SHUREN. It does.

Mr. SHIMKUS. Could you provide those names to us? Not now.

Does this panel have any entrepreneurs and investment and venture capital experts?

Dr. SHUREN. Not specifically.

Mr. SHIMKUS. Does this panel have any patient or patient groups who are in need of products currently under the 501(k) system?

Dr. SHUREN. They do have people with connections with the patient community.

Mr. SHIMKUS. And I would like their names, too, because I don't believe you do.

How much taxpayer money did you give this IOM panel?

Dr. SHUREN. I will get back to you on the exact figure.

Mr. SHIMKUS. Mr. Hall, do you believe the IOM panel is qualified to make decisions on the 501(k)?

Mr. HALL. I think the current members are each individually very talented. I am concerned that the committee does not have patient representation, does not have representation from entrepreneurs, the people that fund this, industry groups, et cetera. And if you look at other IOM committees, such representation is often there.

Mr. SHIMKUS. Thank you, Mr. Chairman. I yield back my time.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Pennsylvania, Dr. Murphy, for 5 minutes.

Mr. MURPHY. Thank you, Mr. Chairman.

Dr. Shuren, a couple of questions for you, and this relates to some areas of jurisdiction for FDA and given the limitations of funding and trying to stretch yourself in many ways.

I am looking here on the Web site, the FDA states it will regulate devices used in the, quote, "cure, mitigation, treatment, or prevention of disease," unquote.

I am curious, if a kit is used by an employer to test or screen for the presence of drugs, would that be a "mitigate, treat, or prevent" disease category?

Dr. SHUREN. Yes. And we have been regulating those devices for about 20 years.

Mr. MURPHY. What kind of tests?

Dr. SHUREN. These are both laboratory-based tests and point-of-care tests, so tests that are actually used in the workplace.

Mr. MURPHY. And are they used to treat or diagnose?

Dr. SHUREN. Yes, if they are not used right, then people actually who should get treatment get missed. People who may have an addiction get missed, and they pose a risk then to the employees. Or they get false results, and they wind up losing their employment.

Mr. MURPHY. Do those tests—are they used in such a way that a single test can cause them to lose employment, or are they followed up? And if there is a follow-up, is that one that really deals more with the employment issue or the treatment issue?

Dr. SHUREN. Well, I was talking about consequences. But what follow-up is done is actually up to the place that is conducting the test, whether or not they do a follow-up or not.

Mr. MURPHY. You also have situations, however, that—are they used to promote, on the other hand, an orderly workplace environment or to deter drug use?

Dr. SHUREN. How it may be used by individual companies, I don't know. But we have regulated it because of the safety concerns that occur when those tests are inaccurate.

Mr. MURPHY. When they are inaccurate. What would be an inaccuracy level that you would consider to be acceptable?

Dr. SHUREN. What it comes down to is, is it actually measuring the drug of abuse or not? And that gets set depending upon the

kind of tests we have. One of the biggest issues now is with the saliva test. We have one that is point of care for saliva that is actually pretty good. The rest that have come through are actually very poor. They have a very hard time detecting drug.

Mr. MURPHY. What is the point-of-care test that is pretty good? Which one is that?

Dr. SHUREN. I will get back to you with the actual name.

Mr. MURPHY. Okay. Of course, we also know that if one is limited from using these tests—there are differences—collecting different types of bodily fluid—saliva, urine, blood, et cetera—and some more invasive in the workplace than others and require more staff time, et cetera. There is a difference between those or just a first-level screen and those that—some that are sent on to the next level.

You would agree with that, wouldn't you?

Dr. SHUREN. Yes, there is a difference between the different tests.

Mr. MURPHY. Now, I know that the FDA has threatened to shut down operations for several American manufacturers making this saliva equipment but not foreign ones. Are you familiar with that?

Dr. SHUREN. We have actually been sending warning letters to a variety of different companies. I will tell you, for the companies now that we have looked at, one of them we had been—or, actually, two of them we were working with very closely. They had committed to actually get us the data. We held off taking an action for many months to let them get the data that they committed and said, "We have it, we will get it to you," and then they didn't get it. And some said, "Oh, yes, we had data, but it is gone."

Mr. MURPHY. Well, my understanding is some of these companies are asking for sufficient time, because you are asking for a lot of data. Will you work with them and find out if they need additional time, if they are indeed moving forward on that process, or is the door closed?

Dr. SHUREN. We actually had been working with them. We gave them lots of time. In fact, we are past the time when—well past the time they were supposed to get back to us. We have had frequent conversations.

But for one of them, they actually did make progress, and they sent us the data. For another one, we have actually seen absolutely no meaningful progress.

Mr. MURPHY. I understand that part of what the guidelines that were sent to these companies were the guidelines for urine-based tests and not saliva-based tests. Now, we are getting into weeds in this a lot here, too, but part of the understanding that I have of these companies is they are—recognized there are really different procedures involved with both of those. I am sure you understand that, as well. And I would hope that there would be some—I mean, from what I understand, they requested fresh guidance in September of last year and wonder when you are going to get them the proper guidance on this saliva-based test.

Dr. SHUREN. Well, we did one better. We have actually been talking with them and walking them through exactly what they need to do, because we have experience with these kinds of tests. But they have opted not to follow what we asked them to do.

Mr. MURPHY. That is not my understanding. And I hope that we can somehow bridge a communication gap here, that you will work with them. Because, look, none of us want to have drug abuse in the workplace. We are familiar with it—the drug problems, workers' comp problems, injuries, deaths, et cetera, at the workplace, the high risk on all sorts of levels when people operating heavy equipment or dangerous equipment are involved in other things.

And along those guidelines, what I understand is there are a number of snags that are perhaps not reaching your level, some of those communication issues. So I would hope that we could talk offline more directly and see if these problems can be mitigated themselves, along those lines.

Dr. SHUREN. We would be happy to come and brief you on what we are doing further.

Mr. MURPHY. Thank you. I would appreciate that. That you very much.

I yield back. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member emeritus, the gentleman from Michigan, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Thank you, Mr. Chairman.

This question is to Dr. Shuren for a "yes" or "no."

You are familiar with the cuts being proposed by the majority in the FDA budget, are you not?

Dr. SHUREN. Yes, I am.

Mr. DINGELL. You are also familiar with the cuts proposed for the device center, are you not?

Dr. SHUREN. Yes.

Mr. DINGELL. All right. Will the cuts in the case of FDA have an impact on the way the Food and Drug can review devices and oversee device safety, yes or no?

Dr. SHUREN. Yes.

Mr. DINGELL. Will these affect the amount of time it takes you to review a device application, yes or no?

Dr. SHUREN. Yes.

Mr. DINGELL. As you know, this committee will be authorizing the Medical Device User Fee Act next year. Does FDA have the staff it needs to approve the devices in an efficient time frame, yes or no?

Dr. SHUREN. No.

Mr. DINGELL. How many does it have?

Dr. SHUREN. In the program right now, we have about 1,250 full-time employees, and then we have additional contract support. That is for the entire——

Mr. DINGELL. How many of those are actually involved in the review and approval of the devices and in overseeing of device safety?

Dr. SHUREN. About 72 percent are involved in what we call the device review process.

Mr. DINGELL. How many do you need?

Dr. SHUREN. We need a lot more. And much of it will depend on the kind of program——

Mr. DINGELL. I am asking for a specific number.

Dr. SHUREN. It will depend on the program we put together. And one of the things we will talk about——

Mr. DINGELL. All right. I will submit a letter and I assume that you will respond, giving me an answer to the questions raised.

Does FDA have the user fees it needs now to approve devices in an efficient time frame, yes or no?

Dr. SHUREN. No.

Mr. DINGELL. Are there any diversions in any of the proposals of the budget to divert money from user fees either in prescription pharmaceuticals, over-the-counter pharmaceuticals, or in the case of devices?

You can submit that for the record.

Dr. SHUREN. We will submit it.

Mr. DINGELL. Would increased user fees help FDA to assure the safety and effectiveness of devices?

Dr. SHUREN. Yes.

Mr. DINGELL. Would they assist Food and Drug in providing more expeditious service to the people in the industry who have these devices up for approval?

Dr. SHUREN. Yes.

Mr. DINGELL. Do you believe increased fees are needed to expedite the review process to benefit the industry?

Dr. SHUREN. Yes.

Mr. DINGELL. Mr. Chairman, I note I have 2 minutes and 10 seconds, and I yield back.

I will look forward to working with you some later time.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Kentucky, Mr. Guthrie, for 5 minutes.

Mr. GUTHRIE. Thank you very much.

Thank you for being here. And I was at a second committee of this subcommittee of this committee, so I apologize, I missed some of it. But I get the gist of what we are talking about.

And I am from a manufacturing background, automotive parts, not medical devices, but I understand getting products to market and being competitive is important. And I want to go just a little different, because I have heard the testimony, and some questions I was going to ask have been answered. And it is appropriate in this subcommittee, because just the other day we were debating a bill about doctors' conscience, and the minority side brought up an objection to the bill, saying, if we pass the bill, it was going to raise taxes and put people out of business.

And so my question—I think it is appropriate in this committee, even though it is not our jurisdiction, to look at what happened during the health-care law. I think those of you who manufacture devices are aware there was a 2.3 percent tax on revenue, not on income, on revenue, which as an effective tax rate, I don't know, you would have to recalculate, but far higher than 2.3 percent. And it goes into effect—and it is $20 billion coming out of the medical device over the next 10 years—it goes in effect in 2013. And even if you are growing your business and trying to put seed money back in your business, you are not making a profit, you still pay this tax. It comes off the top. It comes off the top.

And I would like just particularly Dr. Makower or Mr. Deem or anybody else that is manufacturing, would you describe how this tax affects large and small device companies and how it affects innovation and job creation? Because there was some concern about

our bill last week about what it is going to do to job creation. I would just like to hear what you think this tax is going to do to job creation.

Dr. MAKOWER. I am glad that you asked that question. It is absolutely imperative—absolutely imperative—for small companies that we find a way of modifying that tax proposal. Because, right now, companies that are bringing a new, innovative medical product to market need to get to about $70 million to $100 million in sales before they see dollar 1 of profit.

This means, during the entire time, which may be over several years, under the current proposed law, that they would be paying money to the government simply for the privilege of doing business in the United States without earning any profit here. And that means that they would have to raise more money and/or cut jobs or reduce other ways of expenditure—research and development, other important things for this country.

And so this is—I am very glad that you brought it up. It is absolutely essential for innovation, especially for medical device technology, that we address this important issue.

Mr. GUTHRIE. Mr. Deem?

Mr. DEEM. I would echo Dr. Makower's comments. I think it is absolutely going to result in slowed company growth, delayed hiring, and delayed expansion of the company, without a doubt. I mean, just taking that money right off of the top, it is essentially shunting it right out of the operations that that company needs to grow.

Mr. GUTHRIE. Are you already hearing—I mean, you have to be, because you have to be planning for it—are you hearing your business, businesses in your community, associations that you deal with, how this is affecting them today or as they prepare for it in 2013?

Mr. DEEM. We are hearing a lot of discussion about it. My companies, actually, have been taking so long to get through the regulatory process. Out of the 14, we only have one that is actually selling product right now. But that one actually is planning on trying to figure out what it means to them. Are they going to have to raise more venture capital? Which, in effect, just shunts that straight over to the tax. Are they going to have to try to finance it out of other avenues that will further slow the growth?

Nobody really has a good answer for it. The only thing that we are absolutely sure of is that it will slow growth and it will delay job hiring.

Mr. GUTHRIE. My understanding, too, is some States have what they call business purpose taxes. A lot of States who put them in all of a sudden take them off because their businesses move elsewhere.

There probably are other people that get off-the-top revenue taxes. I am not saying there are not industries that are treated—but I think you all are especially treated differently than most businesses in this country.

And only since the other side brought up the other day that they wanted to work with us to make sure that we had had a productive Tax Code out of this health-care bill. I think this is something—

hopefully, though, they are going to stick with us and get this fixed for you guys.

I know you all answered the question, but does anybody else want to comment on that?

Well, Mr. Chairman, I am about of time, so I yield back.

Mr. PITTS. The chair thanks the chairman.

Now, in the queue we have Lance, Cassidy, and Blackburn, in that order. So the chair recognizes the gentleman, Mr. Lance, for 5 minutes for questioning, then Cassidy.

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

I apologize for not being at the entire hearing. There are two subcommittees today meeting at the same time. And since I have been on the full committee for a month, I try to make both subcommittees. But I certainly appreciate your being with us.

To follow up on what Congressman Guthrie has said, Mr. Deem, I represent the district in this country that has more medical device and pharmaceutical employees than any other district anywhere in America. And the medical device excise tax, I think, will be extremely harmful, especially to the district I serve—we would like to think we are the medicine chest of the country and perhaps the world—and certainly, I think, moreover, harmful to the Nation as a whole.

For example, C.R. Bard is one of the 10 largest manufacturers of medical devices. It is located in the district I serve. And I have been told by leadership there that the new 2.3 excise tax will cost that company $45 million a year, which is 25 percent of that company's research and development budget. This is just one example; there are many across New Jersey and across the Nation.

Could you explain in a little greater detail, following up on Congressman Guthrie, what you believe this will do to the competitiveness of the industry in this country, as it affects the entire world?

Mr. DEEM. Thank you for the question.

I agree with the gentleman, ladies, from C.R. Bard. I think that there are only a few other places where the larger companies are going to be able to trim that in, trim that money out. And when you look at the large company balance sheets, the R&D line typically involves both R&D and regulatory and clinical. And so, if you look at the device tax coming off of R&D, it is hitting them both ways.

Mr. LANCE. And I, of course, believe we should not enact it, that it should be repealed. And I, along with others, were working on that issue.

Do you think that the consequence might occur before the actual implementation of the tax, given the fact that companies will have to begin to calculate what is coming in another year or so?

Mr. DEEM. Absolutely. I haven't worked in the larger companies, but even in the smaller companies, as we look at sales ramps and we look at how quickly we are going to be able to make adjustments, you have to start planning for it now. So already we are delaying hires, and we are looking at how quickly we can grow. And I am sure that is happening to a much, much larger scale in the larger companies like Bard.

Mr. LANCE. Thank you.

Last week, The New York Times reported on a patient who had traveled overseas to receive a medical device that was developed 40 miles from her residence.

To any distinguished member of the panel, I would like to think this is an isolated incident, but I am wondering what the panel's view might be on that.

Dr. REDBERG. You know, I actually am grateful to the FDA for doing its job in protecting the safety and effectiveness of my patients and your constituents. And I think that that device, if it had been shown in clinical trials to be safe and effective, would certainly be approved by the FDA.

Unfortunately, there are numerous records of devices like that—I believe it was a spinal disc—and other ones that have been approved in Europe and have been subsequently shown to have severe problems.

And, remember, we are now talking about implantable devices. And so, I want to know, before the FDA approves a device, that—before we can even talk about safety, I think the number-one goal is effectiveness. Because I don't think you or I or anyone want to have something permanently implanted in me that has never been shown to be effective.

That does cost money, to do a clinical trial to show a device is effective. But I think before we can even start talking about innovation or anything else, I have made a contract to take care of my patients by doing things that will improve their health. If I am going to be put in a position of having to advise them to put in devices that have never been shown to be effective or safe, that it is not something I can advise them on.

So I would think that——

Mr. LANCE. Thank you.

I yield back the 1 second I have left. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Louisiana, Dr. Cassidy, for 5 minutes for questions.

Dr. CASSIDY. Thank you.

And to whomever I speak to, if I interrupt you, I am not trying to be rude. We just have 5 minutes.

To the two cardiologists, I am a gastroenterologist, so I approach with trepidation, okay? But in Dr. Shuren's testimony, he speaks about the necessity to establish effectiveness in the U.S. versus EU, using the specific example that the manufacturer must show that the laser incises heart tissue and also treats arrhythmia in the United States, whereas in the EU you would only have to show that it incises heart tissue only.

But I assume he is talking about some sort of AV node malformation. And, frankly, that is in anatomy and physiology, that if you cut that baby, you are going to interrupt the flow of current. That is an electrical current issue.

So I am just tossing that out, not to challenge, frankly to understand from two cardiologists, does it matter how you cut the AV node?

Dr. NISSEN. I would be happy to take that one on.

Look, it does matter. And it is not just that it cuts; it is that it cuts that right tissue and doesn't cut something that it shouldn't cut.

Dr. CASSIDY. Now, there is a fairly defined—again, I am a gastroenterologist, so with trepidation I say it is my understanding there is a fairly defined anatomical pathway. Granted, there is variance. But, you know, you are going to be a millimeter deep, you are going to be a centimeter wide. Granted, maybe there is scarring with one and not with another, so there is an ancillary. But I assume that, as commonplace as this has been, particularly at the Cleveland Clinic, that you guys know this.

Dr. NISSEN. Yes. We probably do more of these ablations just about than anyplace in the country. And there is a complication rate, and these complications are really serious. And before we would——

Dr. CASSIDY. Now, I don't think you—but that is a different question than effectiveness, correct?

Dr. NISSEN. Well, you know, safety and effectiveness can't be taken apart. You know, if you have a device that ablates tissue but it causes tamponade if it perforates the heart——

Dr. CASSIDY. Now, but safety and effectiveness are different because if you—and I thought Mr. Hall's comments were well-taken. There is an immediate, kind of, you-do-the-procedure-type complication that is one further down. Clearly, these guys are not going to approve something which caused a high incidence of tamponade.

Dr. REDBERG. I would say, you know, you are talking about ablation, which, as you know, has been approved here as well as in Europe.

Dr. CASSIDY. And I just used that example because he used it specifically.

Dr. REDBERG. The Europeans, you know, just published their 5-year experience and shown that only 25 percent of all their patients who got the ablation by the guy who invented it are actually free of atrial fibrillation 5 years later. A lot of those patients have had adverse events, including death, as a result. There is a 1 percent incidence of death reported with that.

And so, again, it is a great example, because you would think, sure, that is a defined part of tissue, easy to do. People are not that simple, and procedures are never perfect. Every procedure has benefits as well as risks. And unless you do a clinical trial and actually follow those patients to something clinically meaningful, if I burn that piece of tissue and you are dead, you are hardly going to have considered that an effective procedure.

Dr. CASSIDY. No, I accept that. So what is the normal rate of failure of ablation, however it is done normally, whether it is scalpel or whatever?

Dr. REDBERG. The 75 percent failure at 5 years.

Dr. CASSIDY. That is with current technology.

Dr. REDBERG. Current technology, and that is most people are getting two or three ablations.

Dr. CASSIDY. By the way, several people from Baton Rouge have gone to Cleveland Clinic, so I am going to accept that as a commentary upon those guys.

Dr. REDBERG. One of the best in the country.

Dr. NISSEN. We do better than most.

Dr. CASSIDY. Okay. You are at 35 percent. But——

Dr. REDBERG. That is at UCSF.

Dr. CASSIDY. Now, frankly, Dr. Nissen, it looks like Hall's methodology in his paper is superior to yours.

Dr. NISSEN. Actually, it is faulty. His denominator, he used all submitted devices. And——

Dr. CASSIDY. But when I go back, I was actually looking at, okay, he did the kind of peri-approval period as a high-risk recall. And then he did the late high-risk, which is unrelated, if you will, to the approval process. The approval process is not going to catch the complication 5 years down the road.

Dr. NISSEN. It may or may not. It depends on what the mechanism, the complication is.

Let me say that we have the same numerator. He has a different denominator. His denominator is all submitted devices, and that is not a realistic denominator. It is actually approved devices that is the denominator.

Let me put it to you this way, Dr. Cassidy. If you have a 99.5 percent success rate, that sounds very high. But tomorrow when you get on a plane to fly home to Louisiana, if the pilot gets on and says, "There is a 99.5 percent chance that the plane will take off and land successfully," would you get off the plane or would you stay on the plane?

Dr. CASSIDY. I accept that. And I am almost out of time; that is the only reason I interrupt.

But, Mr. Hall, could you respond to Dr. Nissen'sdiscounting of your findings?

Mr. HALL. Sure. I think the key is to try to identify the reason for the recall so you can try to fix the problem. And if you just look at the numerator, how many, that doesn't tell you whether you have a big problem or a small problem, and, most importantly, it doesn't tell you how to fix it. So if you have problems that are not related to the pre-market process, changing the pre-market process is going to be useless exercise.

And the comments earlier about funding, et cetera, I don't like this comment of more or less regulation. I believe in appropriate regulation. And, therefore, put the dollars where they have the leverage, and that is what my study attempted to do.

Dr. CASSIDY. I thought that was a very good point. I wish I had more time to ask you all. Thank you for your testimony.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Georgia, Dr. Gingrey, for 5 minutes for questions.

Dr. GINGREY. Mr. Chairman, thank you very much.

I will get right to the questions. I want to address them primarily to Dr. Makower. According to a 2009 report by Ernst & Young, access to venture capital by medical technology companies dropped 18 percent in 2008 due to the United States economic crisis.

Dr. Makower, how important is venture capital to medical device innovation and development?

Dr. MAKOWER. Venture capital is the lifeblood of innovation in med tech, absolutely.

Dr. GINGREY. A Pricewaterhouse Coopers study released last month found that, and I quote them, "The innovation ecosystem for medical device technology, long centered in the United States, is moving offshore, and medical technology innovators are going outside the United States to seek first income."

What is first income, Dr. Makower? And why do companies feel they need to go offshore to get first income?

Dr. MAKOWER. I think what you are referring to is the approval-of-origin requirement that many countries are requiring. In other words, many countries will not allow you to sell a product in their country unless you have at least achieved approval in your own country.

And the impact of that for a U.S. manufacturer is this, that if we are delayed in getting approvals here, we can't even sell other places in the world unless we move the manufacturing facilities to other countries. And that is why this is so——

Dr. GINGREY. If you will allow me to interrupt, I think that what you are referring to what have been my next question. In fact, I will talk about it a little bit, country-of-origin——

Dr. MAKOWER. Country of origin, right.

Dr. GINGREY [continuing]. Requirements. That was not this issue of first revenue. But, yes, you are absolutely right. I think, by 2020, the authors of this Pricewaterhouse Coopers study predict that China, India, and Brazil will gain significantly in key device measurement areas, while the United States will continue to lose ground.

And, interestingly enough, as you said, these countries also—many countries, not just these—but they have that country-of-origin requirement, that it requires any device manufactured in the United States first be approved for sale in the United States by the FDA before it can be approved for sale in the home market.

Dr. MAKOWER. That is right.

Dr. GINGREY. So this is what you were referring to in regard to the country of origin?

Dr. MAKOWER. That is exactly right. And that is the reason why manufacturing plants and high-paid jobs are leaving the country.

Dr. GINGREY. These jobs, by the way—that brings up another point. When a medical device company does pick up and move, for whatever reason—I think many of those reasons have been outlined by my colleagues in the questions and certainly by the witnesses. And when they move overseas, what type of jobs are we losing? Are these minimum-wage jobs? Are we losing scientist and other highly technical and high-paying jobs to our competitors?

Dr. MAKOWER. Exactly. As you pointed out, they are high-paid jobs. They are scientists, they are engineers. They are the very, very sought-after jobs that are moving.

Dr. GINGREY. Well, how do—in fact, anybody can answer this question—but how do EU device regulatory systems compare to the United States? Are the EU regulations more predictable and certain? Why does that matter to a device firm?

Dr. MAKOWER. It is more transparent. You know what you need to do, and that is why it is more straightforward.

Dr. NISSEN. They are also much weaker. They don't require that you demonstrate efficacy. And we think that that is important. If

you use a device, you want to know that it is actually going to work. And that is not required in the EU.

Dr. GINGREY. And I think, Dr. Shuren, you wanted to respond.

Dr. SHUREN. Because in the EU, the public can't—there is no transparency. These are what is cut between the company and the private company. In fact, the European Commission said—and they are relooking at their system—experience indicates that the current system does not always offer a uniform level of protection of public health in the European Union. New and emerging technologies have challenged the current framework, highlighting gaps and pointing to a certain scarcity of expertise——

Dr. GINGREY. Yes, yes, but, Dr. Shuren, I guess cutting right to the chase on that, and I will ask you specifically, does the EU have more safety problems? You are, I think, suggesting that their system is more lax, and that frightens you. But, really, statistically, are they having more safety problems?

Dr. SHUREN. I think the data that is out there—there are two very different systems. They don't have enough data out there to actually make a firm comparison. But we do have some evidence to show that the U.S. system does provide great value.

Dr. GINGREY. Well, I think that is kind of an anecdotal sort of response.

Let me just say to this you, as I conclude. I want you to know that I appreciate the work that the FDA undertakes for American patients. I am a physician, too, an OB/GYN doctor. But I do believe that if we don't undertake an immediate and very critical review of the FDA regulatory process, trying to identify safe and effective ways to improve the transparency and consistency of the approval process, irreversible damage to the United States-based medical innovation will result.

And, you know, we are in a situation where we need jobs, we need them desperately. I realize that the balance is hugely important, but we need to smooth and streamline this process and not keep changing the bar.

Mr. Chairman, thank you for your indulgence, and I will yield back.

Mr. PITTS. The gentleman's time has expired.

The chair recognizes the gentlelady from Tennessee, Mrs. Blackburn, for 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

And I want to thank you all for being here.

My district in Tennessee includes a city you all probably know a little bit about, Memphis. And, as you know, we are probably the number two when it comes to device implementation, creation. And with our companies that are there that are doing tremendous work in R&D, with patent holders, with the biotech R&D that is being done in the mid-part of Tennessee, the other end of my district, we hear a lot about the FDA and the problems that exist with the FDA.

And we are focused on this, because we think that in the 21st century, when you look at the creative economy as it exists and look at jobs creation and jobs retention, that we have to make certain we are protecting the intellectual property of these innovators

and creating the environment that they can innovate here but also that they can manufacture here.

And, Mr. Makower, I know we have talked about your study and everyone has focused on this in our questioning, but I think it is such an imperative that we create the environment that our companies and our innovators can handle that jobs growth. And I liked what you did when you analyzed the FDA's impact on medical technology innovation and comparing the EU and the U.S., the time and the cost and lack of predictability.

But what I would like to do is—we look at jobs, 400,000 Americans and over 2 million jobs that are created through this industry. Where is the FDA causing us problems and hindering on that? What other countries around the world, specifically especially in Europe, are trying to take our jobs? Who is trying to compete with us on this environment? How do we reach that standard so that we are responsible to consumers but we are not hampering innovation?

So, quickly, if you will hit what you think our problems at the FDA are and how they get in the way of those job creation numbers that we want to see and the environment for jobs growth to take place; and then I am going to let any of the others of you weigh in, also.

Dr. MAKOWER. The fundamental themes that we have been talking about are predictability, reasonability, transparency. Those are the things that allow the process to happen. Because when you go to raise money as a small entrepreneur, you can set out a path. You know what is expected.

Mrs. BLACKBURN. And you see the FDA as a hindrance.

Dr. MAKOWER. Right now, that is a problem. In other countries, it is clear. It is clear what you need to do, and it does not take as much time.

Mrs. BLACKBURN. Compare to me if I were to take an implement for a hip to the FDA. In the U.S., the time to get it through the FDA would be what and in Europe it would be what?

Dr. MAKOWER. It is a specific example, and I don't want to misstate what the times would be for that. So I would get back to you on the exact numbers.

Mrs. BLACKBURN. That would be great. I think it would be helpful.

Mrs. BLACKBURN. Because we are looking 10, 20 years down the road; and we are concerned about what would happen with the medical device implementation industry here in this country. It is a lot of jobs for us here in Tennessee.

Anybody else want to weigh in with the problems with the FDA or how they see the FDA as an impediment to jobs retention and jobs growth?

Mr. DEEM. I think one of the things that has been touched on from time to time but it deserves significant thought is the risk benefit ratio. That has always been a concern, and that is clearly the most difficult job that the agency has, is determining where is the appropriate balance between risk and benefit.

I think if we look over the last several years and look at the delays that have increased and the inconsistency that has crept in, I think it has a lot to do with what is our expectation of risk and

benefit. So I think that is an area that we as a people should look at as well.

Mrs. BLACKBURN. Do any of you know of any specific firms that have chosen to move offshore for manufacturing? Could you provide those examples?

Mr. DEEM. It is not one of my companies, but there is a company named Biosensors which is a worldwide stem company. They had a headquarter in—it was either Irvine or San Diego. They were being held back from expanding into international markets that they wanted to go to by the country of origin laws, and just within the last year they ceased all U.S. Operations and moved their jobs overseas.

Mrs. BLACKBURN. How many jobs was that and how much on average do they pay?

Mr. DEEM. I would have to get back to you on the specific number of jobs, since it wasn't my company. But the average pays for the types of manufacturing that we are talking about can be in the 40, 50,000—it is very high-paid manufacturing. And then when you start to look at the engineers that are involved, you are in the hundred, $150,000 jobs. So these are very, very highly sought after, high-pay jobs.

Mrs. BLACKBURN. Thank you. I yield back.

Mr. PITTS. Did any of the other witnesses wish to respond to that question?

Dr. Redberg.

Dr. REDBERG. I just wanted to point out the other side of the money that we spend in the over $100 billion on devices is that when we are approving devices that haven't been shown to be of benefit to your constituents and our patients, that means we are spending billions of dollars. Technology is the number one driver of health care costs. And the reason that a lot of jobs are having issues in employment and State governments are because they cannot sustain the costs of health care premiums.

So I would just consider the other side of allowing untested, expensive new technology of no known benefits, definite risks is also driving up health care premiums and driving businesses to close, because they cannot afford to pay for the health care for their workers.

Mr. PITTS. Dr. Shuren.

Dr. SHUREN. And I think it is also important to recognize, and we know we have a role to play, and I have mentioned there are actions that we are taking, but this is far more complicated. Even Advenet has talked about the health of the medical device industry, and I don't want to put things down. But we went through the biggest recession since the Great Depression. It has affected everyone.

But in the medical device industry, they changed their business models. They became more risk averse. The venture capitalists have decided we are not going to invest so much in the early stage innovative technologies. We want to see this more fully developed. They raised the bar on their own industry.

I don't think the answer to this is that we change the American standard that we have had in place that has served the country very well. We agree that we need to have the right balance be-

tween facilitating innovation and assuring that devices are safe and effective.

We are stepping up to the plate for things that we need to do. If this is really going to happen, we need industry to do the other part of it; and we also do need to have the people do the job right. Even industry has said, and Josh has said, we have high turnover. They find that that affects reviews, and we agree. But the problem is we don't have the people doing the work. Their workload is overloaded, and we need to address that.

If we are really going to make this right, we have to invest. We have got to invest in the FDA. If we want to be competitive to industry, we need to be competitive about the FDA brand.

Mr. PITTS. Thank you.

Any other witnesses wanted to respond to that question?

Mr. HALL. Just one thing.

There seems to be a belief there is a yes, no, or binary aspect to the 501(k) system. I want to clear up.

The agency has the authority to obtain clinical data under the 501(k) system. They have the statutory authority, they have the regulatory authority in cases in which they think that is necessary or appropriate to make safety and efficacy determinations. So they have that authority right now, and probably 10 to 15 percent of submissions include clinical data of some sort.

Mr. PITTS. The chair thanks the witnesses.

Dr. BURGESS. Mr. Chairman, I ask unanimous consent just to ask one follow-up question.

Mr. PITTS. Without objection.

Dr. BURGESS. Dr. Shuren, I just wanted to point out that last summer when Dr. Sharfstein was here we had a hearing on bottlenecks in the pipeline, and I asked a question because I was concerned. We gave $10 billion to the NIH for the stimulus. We gave it. I voted against that. But Congress gave $10 billion to the NIH.

And I asked Dr. Sharfstein, is this going to be a problem as all of this new stuff from NIH starts coming down the pipeline? Is FDA—what are you going to do? And he was dismissive and said that they had all of the money that they needed.

This past summer, with the hearing on the DeCoster Egg Farms, with the salmonella that appeared in the eggs, that it appeared that in the food safety aspect, which I know is not your jurisdiction, but it appeared that some very basic processes were not followed, and communication between FDA and USDA really suffered. And he told me once again that funding was not the issue. It was a process.

So I just wanted to make those points. Because I have asked at the highest levels of the FDA, are we giving you the tools that you need, given the fact of everything else that is going on around you? And was told twice by the second in command at your agency that that, in fact, was not an issue.

I recognize he is no longer the second in command at your agency.

Dr. SHUREN. I don't know what was said.

I will tell you that now, for the first time, in fiscal year 2010, the FDA, which is a lean agency, for the very first time exceeded its FTE counts, its full-time employees that we had on board 18

years ago in 1992. Just was coming up to speed then. And, in the interim, medical devices have become significantly more complex and challenging.

If we honestly want to be—remain the innovators, the world's innovators, we have to address all of the issues. When FDA approves a product, other countries listen. You can get a CE mark—and I talked to my folks over there, and their slow uptake on the new technologies because they don't have full confidence on the CE mark. Some will use it. A lot won't.

But when the FDA approves a device, not only is there rapid uptake here in the U.S., other countries take notice, and the physicians over there start to use it. We need to invest in the FDA. It is so critical that we are working well, because it ultimately helps them and it helps patients. And, as a physician, I care a lot about that.

Dr. BURGESS. As do I.

The last thing. You have made a comment that industry just won't talk to the FDA. Again, you do have industry there, Mr. Deem, Dr. Makower. You have a chance now to talk to the FDA. They are right there. So maybe you guys could just visit a little bit and get some of these things hashed out.

Mr. PITTS. Okay. Dr. Burgess, would you yield to Mr. Pallone?

Dr. BURGESS. Absolutely.

Mr. PALLONE. I know we haven't had a chance to ask many questions on this side.

Dr. Shuren and Dr. Redberg, there was a lot of discussion on the study released this week about the—Dr. Nissen I said? I am sorry. Dr. Nissen and Dr. Redberg, there was a lot of discussion about the study released this week about recalled products under 501(k). I am not sure that you had a chance to respond to that, if you would. I will just give you some time to do that.

Dr. NISSEN. You know, what I want to say is that there is a serious problem here. One hundred and twelve million devices were withdrawn over a 5-year period of time, more than 2,000 deaths a year due to device failures and more than 100,000 injuries. That is serious, and it needs to be looked at very carefully. And so keeping that balance between safety and rapid and speedy approval is really critical.

And what I am arguing for is not to make things tough on industry. It is to make things safe for patients. Putting patients first. We have a motto in medicine: primum non nocere. In Latin, it means above all do no harm. And a device that has to be withdrawn, taken out of a patient's body, whether it be a spinal disk or something else, is very serious.

The final thing I wanted to say—I didn't quite get a chance with Dr. Cassidy's question—is this idea that there is a 99.5 percent success rate for 501(k). And here is what I want you all to think about when you go home on Friday night.

You get on the plane and the pilot comes on and says there is a 99.5 percent chance that this plane will take off and land safely. Is that good enough or is it not good enough? I don't think it is good enough, and I think we can do better.

Dr. REDBERG. I would like to also point out that recalls, while they are important, they are not a way to gauge safety of medical

devices. Recalls are the tip of the iceberg. Because of the adverse event reporting system, it is estimated that we only know about 1 or 2 percent of all serious adverse events that occur.

So while recalls are an extreme example, because a device has not been recalled, it is not an assurance of device safety and, more importantly, it is not an assurance of effectiveness.

So, again, the FDA's primary mission, while encouraging innovation is important, but not to encourage innovation at the price of ignoring safety and effectiveness. And the only way to know a device that I am going to put in your body is safe and effective is to study it in clinical trials in humans with meaningful endpoints, real outcomes, and reasonable follow-up and continued post-marketing surveillance so that those rare adverse events can be reported. We have a long way to go to get to that goal.

Mr. HALL. I think it is clear that everybody is interested in safety. If you want safety, you need to understand the reasons why the problem occurred; and the majority of those recalls occurred because of after-approval issues, not because of the premarket system. And I believe in targeted or focused legislation.

If you go to the 99.5 would you get on an airplane, with that analogy you would never go to the hospital, because the hospital rates of problems are much greater. 2.3 percent of Medicare patients have a safety issue in the hospital; 15 percent of elders get a BIS prescription. We all need to do better.

Mr. PITTS. Excellent testimony.

I don't want to cut you off. Did you have something to say, Dr. Shuren?

Dr. SHUREN. All I would say is we take the safety concerns very seriously. And in fact, the data shows that there are problems that are occurring that could be addressed premarket. We have tried to address some of this in the actions we are taking. There are times when targeted manufacturing data for certain products can help us identify problems beforehand and in some cases doing the preclearance inspection.

I will say if much of the debate is going to be on quality systems, I would note that in the EU you have the auditors, you have the third parties that go in and they look at the companies who are actually going to bring the product on the market. Here in the U.S., the law sets a very high bar for us to do that. If we are going to look at quality systems and put more of an emphasis, then we should sort of revisit that framework.

And, lastly, I would say there are times when clinical data can actually identify safety problems. With infusion pumps it is exactly what we are going to impose on the manufacturers, and we are starting to do it.

Mr. PITTS. All right. Thank you.

In conclusion, I would like to thank all of the witnesses and the members that participated in today's hearing. I remind members that they have 10 business days to submit questions for the record, and I ask that the witnesses all agree to respond promptly to the questions.

As this Monday is President's Day, members should submit their questions by the close of business on March 4.

The subcommittee is adjourned.

[Whereupon, at 1:10 p.m., the subcommittee was adjourned.]
[Material submitted for inclusion in the record follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

APR 12 2011

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for your letter of March 17, 2011, to Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health (CDRH or the Center) at the Food and Drug Administration (FDA or the Agency), regarding questions submitted for the record by Members of the Committee. These questions are in follow up to the Committee's February 17, 2011, hearing entitled "Impact of Medical Device Regulation on Jobs and Patients." We have restated the questions in bold, followed by our responses. This is a partial response.

Thank you again for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

Michele Mital

for Jeanne Ireland
Assistant Commissioner
for Legislation

The Honorable Joseph R. Pitts

1. **FDA has received significant infusions of funding in recent years. According to the Congressional Research Service, medical device review funding increased from $275M to $368M in just two years from FY08 to FY10. This represents a nearly 35% increase in funding. Is this funding increase accurate? A recent California Healthcare Institute study found that, during the same time period, average 510(k) review time increased by 43% and the average review time for PMA increased 75%. Why have review times slowed so dramatically despite such a significant increase in FDA funding?**

Contrary to the California Healthcare Institute (CHI) study, FDA review performance has held steady or improved for 510(k)s and premarket approvals (PMA). Overall, we are meeting or exceeding the Medical Device User Fee Act (MDUFA) performance goals for over 95 percent of the submissions we review. In the case of 510(k)s, we are meeting both Tier 1 and Tier 2 MDUFA goals.[1] For PMAs, we are far exceeding the requirements of the Tier 1 goal and steadily improving to meet the Tier 2 goal.[2] The Tier 2 goal for PMAs is a "stretch goal" under the amended User Fee Act, i.e., one that FDA and industry agreed was challenging for FDA to meet. However, total review time—the time it takes for FDA to review a submission and for companies to respond to FDA questions—has increased, primarily due to an upward trend in the amount of time industry is spending responding to information requests from FDA. In a recent FDA analysis, we found that the main driver for this upward trend is a decrease in the quality of submissions from industry, causing FDA to ask for information that should have been in the original submission. The most common missing information includes:

- inadequate device descriptions
- discrepancies throughout the submission
- failure to address necessary information as outlined in guidance documents
- problems with the proposed indications for use
- completely missing performance testing
- completely missing clinical data

Regarding PMAs, the CHI study uses "average review time" in its analysis. Because we receive relatively few PMAs (approximately 30) each year, a small number of "outliers" or problematic submissions, as was the case in 2010, can skew the results. Given this problem, the appropriate performance measure for PMAs is the mid-range (or median) review time. Had CHI used that metric, the study would have shown an improvement in PMA review times in 2010 over those from 2009, which is consistent with our performance on the MDUFA goals.

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[1] Under MDUFA, FDA uses a two-tier approach for each submission type. Tier 1 performance goals focus on completing a large percentage (from 50 to 90 percent) of review cohorts in a shorter amount of time. Tier 2 performance goals focus on completing a larger percentage (from 90 to 98 percent) of review cohorts, but over longer time frames. The Tier 1 goal for 510(k)s is to issue a decision on 90 percent within 90 days. The Tier 2 goal is to issue a decision on 98 percent within 150 days.

[2] The Tier 1 goal for PMAs is to issue a decision for 60 percent within 180 days. The Tier 2 goal is to issue a decision for 90 percent within 295 days.

Detailed information about FDA's performance under MDUFA can be found in the 2010 Performance Report to Congress for the Medical Device User Fee Amendments of 2007 at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/MDUFMA/ucm243385.htm.*

2. **In the recent MDUFA report to Congress, FDA review performance is reported in FDA days, not calendar days. For example, for 510(k) reviews, FDA is meeting its performance goal, yet FDA has reported that the total time, in other words, calendar days, to an FDA decision continues to increase. This occurs because the number of FDA review cycles or number of times FDA reviewers stop the review clock is increasing, thus increasing the total review time. As part of another MDUFA performance goal, FDA committed to an interactive review process, which is intended to improve the review process and decrease the total review days.**

   Please describe the steps you are taking to improve the interactive review process and to reduce the number of times reviewers stop the review clock, thus reducing the total days to a FDA decision.

CDRH is currently evaluating ways to improve the interactive review process, which will also reduce the number of times reviewers have to stop the review clock. This has been set as one of CDRH's 2011 Strategic Priorities as follows:

- By April 30, 2011, CDRH will obtain feedback from constituencies about the strengths and weaknesses of the interactive review process.
- By June 30, 2011, CDRH will clarify CDRH roles, responsibilities, and workflow for the interactive review process and improve the business process, if necessary, as well as develop performance goals and accompanying tracking tools.
- By September 30, 2011, CDRH will re-assess the standard roles, responsibilities, practices, and procedures for the interactive review process and implement changes as necessary.
- By November 30, 2011, CDRH will assess its interactive review process performance and modify as necessary to meet interactive review performance goals.

How is "stopping the clock" accounted for when the FDA counts review days?

When FDA has substantive questions or notes deficiencies regarding a premarket submission, we inform the applicant or sponsor and place the premarket submission on hold. This action stops the review clock, pending receipt of the answers. Once the answers are received, the review clock starts again. "FDA time" includes all increments of time FDA spent reviewing a submission.

3. From what I understand, there is significant concern as to how FDA's proposed changes to the 510(k) program will affect applications submitted during FDA's implementation of these changes. How will you ensure that applications submitted during this implementation will neither be delayed nor adversely affected?

It is FDA policy that we not change rules or expectations until after the effective date of a guidance document or regulation. Regulations, and nearly all guidance documents developed by FDA, undergo a notice-and-comment period to provide the public an opportunity to comment on the proposals. FDA then utilizes public comments in its development of the final regulation or guidance. The only exception to this process is when, prior to a guidance or regulation being issued or finalized, new scientific information, such as a previously unknown safety concern, comes to light and needs to be incorporated into FDA's current evaluation of the safety and/or effectiveness of a new medical device.

In addition, as mentioned in the Plan of Action for Implementation of 510(k) and Science Recommendations, FDA will be sending "Notice to Industry Letters" to clarify and more quickly inform stakeholders when CDRH has changed its regulatory expectations on the basis of new scientific information. You may view the Plan of Action for Implementation of 510(k) and Science Recommendations at *http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM239450.pdf.*

4. Will you assure the Committee that you will not move the goal posts during the clearance process?

Yes, to the extent that this commitment is consistent with our existing policy, we can assure the Committee that we do not intend to move the goal posts during the clearance process. As mentioned in our answer to Question 3 above, FDA generally does not change the rules or expectations for a program or review process until the effective date of a new guidance or regulation. Any exceptions occur on a case-by-case basis and are only warranted if new scientific information comes to light that affects the way FDA assesses a particular product's safety or effectiveness. Of note, the guidance documents being developed pursuant to the Plan of Action for 510(k) and Use of Science generally involve clarification of FDA policies, rather than a response to new scientific information.

Will the rules in place at the time an application is submitted be the rules by which an application will be judged?

Yes, in the majority of circumstances, the rules in place at the time an application is submitted are the rules by which an application will be judged. An exception is when new scientific information has come to light and needs to be incorporated into FDA's evaluation of the safety or effectiveness of a new medical device.

5. How will you ensure that applicants receive proper notice of all of FDA's changes so applicants have enough time to prepare their applications and apply FDA's changes?

Changes will be articulated through the issuance of "Notice to Industry" Letters, new guidance or regulations, or updates to existing guidance or regulations. Regulations and guidance documents developed by FDA generally undergo a notice-and-comment period to allow the public an opportunity to review and comment on the proposals prior to finalization. This comment period usually spans a period of months and allows the public sufficient time to prepare for any changes proposed in the draft guidance or regulation. FDA utilizes comments on the proposed draft versions to develop final regulations or guidance. This process gives all manufacturers who intend to submit a device for clearance or approval notice of current Agency thinking. Regulations and guidances that require industry to make major changes will usually carry an effective date subsequent to the publication date of the final version so as to give manufacturers adequate time to implement the changes; although, FDA may implement current thinking described in a draft guidance document before finalizing on a case-by-case basis.

6. How will you ensure that FDA staff is properly informed of any changes so there [sic] no disruption of the clearance process?

As part of the implementation of our 510(k)/Use of Science Plan of Action, there will be training for FDA staff on any changes in policy, regulations, or expectations prior to the date those changes take effect.

7. Under FDA's 510(k) reform initiative, FDA plans to establish a database of medical device labeling, which would require medical device firms to submit product labeling on a periodic basis. FDA currently has the authority to request that firms submit medical device labeling in response to specific requests. Within the last 10 years, how many times has FDA used this authority to request labeling?

a. Under what circumstances did FDA make those requests?
b. What types of labeling did the agency request?

FDA occasionally makes individualized requests of manufacturers to submit labeling for marketed products to ensure that the labeling describes intended uses that have been cleared or approved by FDA, contains adequate directions for use, and is not false or misleading, as required. Compliance with such requests is not mandatory and FDA does not track such requests, although FDA may obtain such information through a subsequent inspection.

c. What is FDA's process for a sponsor to request and pursue an appeal of a PMA denial?

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), the sponsor of a PMA may appeal denial of approval of a PMA by requesting an open public hearing or a hearing before an advisory panel. The appeal must be filed within 30 days of the denial of approval and must be filed under the procedures described under 21 *Code of Federal Regulations* (CFR)

10.33, "Administrative Reconsideration of Action," which is the regulation that governs requests for reconsideration.

d. What is FDA's statutory response time to a petition requesting an appeal of a PMA denial?

There is no statutory timeframe for responding to a petition requesting an appeal of a PMA denial. Following presentation of the information during the open public hearing or upon receiving the recommendation from the advisory panel, the Office of the Commissioner shall issue an order upholding the denial or reversing the denial and stating the reasons for upholding or reversing the denial.

e. Are FDA's timelines for response and its processes satisfactory and transparent to ensure an efficient and effective appeal process in support of the agency's public health mission?

These statutory provisions create alternative appeal mechanisms for requesting reconsideration of a denial of approval of a PMA. The person requesting reconsideration may seek review in a formal evidentiary public hearing or review by an advisory committee of experts. The formal evidentiary type hearing is an administrative adjudicative proceeding with trial-type procedures, while review by an advisory committee of experts entails appointing panel members with appropriate expertise to provide a recommendation of the reconsideration and other administrative procedures to ensure the fairness of the proceeding. Both of these processes require significant investment of resources on the part of both the Agency and the person requesting review. Imposing timeframes on these processes could interfere with the procedural protections in place to ensure fairness and the time necessary for those making recommendations or issuing final decisions to fully understand the matter under review.

Both types of proceedings are public and, in both cases, the Center makes public beforehand information about the reconsideration. This information includes the review memorandum describing the scientific and regulatory bases for the denial and information about the proceeding.

The Honorable Michael C. Burgess, M.D.

1. I have heard from companies that the FDA doesn't understand evolving science. As medical breakthroughs accelerate, how will the FDA be able to handle and keep up with the number of submissions for approval?

Since the inception of the medical device program, CDRH has kept pace with advances in technology, industry practices, and evolving science. CDRH is made up of dedicated, highly skilled, and internationally respected public health employees, including physicians, engineers, biologists, chemists, physicists, statisticians, epidemiologists, nurses and pharmacologists. These employees work at the forefront of research and are experts in many of the technological areas in which devices are submitted for review.

CDRH aims to maintain cutting-edge expertise and experience in-house, but some technologies emerge so rapidly that it is challenging for the Center at its present capacity to be fully prepared in advance for all devices it reviews. CDRH works to identify and predict developing technologies and to identify sources of scientific expertise to adequately evaluate those technologies through horizon scanning activities, and we are in the process of establishing Networks of Experts that are available to answer questions about new and developing technologies.

The Agency is also taking several steps to ensure that our staff has the proper expertise, or access to experts, required to review new and innovative devices. For example, the Agency is currently determining how to best leverage existing expertise and expedite access to external expertise, how to better maintain and strengthen existing expertise through training, and how to acquire external expertise through third-party programs, such as fellowship programs. However, for FDA to stay abreast of evolving science in the future and to maintain U.S. competitiveness, the Agency will need sufficient resources. This issue is being discussed with industry as part of our dialogue on reauthorization of MDUFA.

In addition, the Agency as a whole recognizes the role it must play for medical technological advances to reach their full potential, i.e., FDA must play an increasingly integral role as an Agency not just dedicated to ensuring safe and effective products, but also to promote public health and participate more actively in the scientific research enterprise directed towards new treatments and interventions. We must also modernize our evaluation and approval processes to ensure that innovative products reach the patients who need them, when they need them. These new scientific tools, technologies, and approaches form the bridge to critical 21st century advances in public health. They form what we call regulatory science: the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products. You may learn more about the Agency's Advancing Regulatory Science for Public Health initiative at *http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm.*

This document outlines a broad vision for advancing regulatory science and unleashing its potential to improve public health. It discusses the role of FDA, working with partners, to strengthen the field, both within the Agency and throughout the Nation.

How does the FDA plan to approve new technologies using old approval guidelines?

FDA believes it is important to update guidances when appropriate, based on new science and as expeditiously as possible. However, because updating guidance is resource-and time-intensive, the Agency's capacity to update guidance is limited. Expanding this capacity is being discussed with industry as part of our dialogue on reauthorization of MDUFA.

Since it would be impossible to judge new devices by old standards, how do you foresee the approval process changing and how long will this process take?

The statutory standard for evaluating devices is "reasonable assurance of safety and effectiveness." We have evaluated, and will continue to evaluate, devices with respect to their

safety and effectiveness, or, for those that have predicates, their safety and effectiveness relative to a currently marketed device. That statutory standard applies, regardless of whether we amend the regulations.

In addition, the Agency is very engaged in the development of domestic and international standards that guide medical device design and testing. These standards establish criteria that may be used to assess the safety and efficacy of devices. We also use these standards as a way to communicate testing requirements to manufacturers. Manufacturer adherence to these standards streamlines the review process.

How will the FDA be able handle the influx of technologies of the future including those in biomedical engineering or biologics if you are having a hard time adapting old methodologies to current science?

The Agency is constantly adapting to address the influx of new technologies. We target our hiring based on current and forecasted specialty needs. However, our ability to hire adequate numbers of experts depends on our level of funding from appropriated dollars and user fees. Funding is being discussed with industry as part of our dialogue on reauthorization of MDUFA. In addition, we are establishing networks of external experts to help us better understand new technologies more quickly.

2. **I saw the FDA's recently released "Innovation Initiative". While I'm glad that FDA is focusing on fostering innovation and promoting American competitiveness, isn't this something that FDA should be doing with every application it receives? Why does there need to be a special initiative? Shouldn't you have been doing this all along?**

FDA's mission includes promoting the public health, which includes facilitating medical device innovation. Most of the proposed actions under the Innovation Initiative would foster innovation for all types of devices. These proposals include:

- streamlining the *de novo* process for new, innovative, lower-risk devices
- issuing guidance to facilitate the use of clinical data generated outside the United States
- establishing a network of external experts to assist FDA in addressing complex scientific issues
- establishing a voluntary third-party certification program of medical device test centers
- developing a core curriculum for device development and assessment to train future device innovators
- establishing public-private partnerships and workshops to promote regulatory science
- enhancing FDA's device horizon scanning efforts so that the Agency is better prepared for new technologies that it will review

One action under the Innovation Initiative, the Innovation Pathway, is more narrow in its proposed scope. The Innovation Pathway will require a greater upfront commitment of resources by FDA, and we can apply this Pathway to a small number of pioneering technologies initially. However, as we stated in our white paper, released in February, and at our March 15, 2011,

public meeting on the Innovation Initiative that, if adequately resourced, we would make the Innovation Pathway available, at a manufacturer's and FDA's discretion, to all or most devices for which a clinical study has to be conducted. The Pathway would not provide additional value for lower-risk devices that do not require clinical studies.

In addition, in January 2011, FDA announced 25 actions it would take in CY 2011 to improve the 510(k) review process. These actions are intended to facilitate innovation for all types of devices by improving the predictability, consistency, and transparency of our premarket review programs.

3. **It's my understanding that the average 510(k) decision time has risen 20 percent from 2002-2008 (97 days in 2002 v. 116 days in 2008). The director recently released a letter emphasizing FDA's dedication to increasing the predictability, reliability, and efficiency of our regulatory pathways. At the time I wrote you with my concerns that you were altering a process without consulting Congress. I will reiterate a question I asked in that letter. How specifically does the FDA plan to do this and why did they undertake changes with IOM still in the works?**

FDA review performance has held steady or improved for 510(k)s and PMAs. Overall, we are meeting or exceeding the MDUFA performance goals for over 95 percent of the submissions we review. In the case of 510(k)s, we are meeting both Tier 1 and Tier 2 MDUFA goals.[3] For PMAs, we are far exceeding the requirements of the Tier 1 goal and steadily improving to meet the Tier 2 goal.[4] The Tier 2 goal for PMAs is a "stretch goal" under the amended User Fee Act, i.e., one that FDA and industry agreed was challenging for FDA to meet. However, total review time—the time it takes for FDA to review a submission and for companies to respond to FDA questions—has increased, primarily due to an upward trend in the amount of time industry is spending responding to information requests from FDA. In a recent FDA analysis, we found that the main driver for this upward trend is a decrease in the quality of submissions from industry, causing FDA to ask for information that should have been in the original submission. The most common missing information includes:

- inadequate device descriptions
- discrepancies throughout the submission
- failure to address necessary information as outlined in guidance documents
- problems with the proposed indications for use
- completely missing performance testing
- completely missing clinical data

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[3]Under MDUFA, FDA uses a two-tier approach for each submission type. Tier 1 performance goals focus on completing a large percentage (from 50 to 90 percent) of review cohorts in a shorter amount of time. Tier 2 performance goals focus on completing a larger percentage (from 90 to 98 percent) of review cohorts, but over longer time frames. The Tier 1 goal for 510(k)s is to issue a decision on 90 percent within 90 days. The Tier 2 goal is to issue a decision on 98 percent within 150 days.

[4] The Tier 1 goal for PMAs is to issue a decision for 60 percent within 180 days. The Tier 2 goal is to issue a decision for 90 percent within 295 days.

Detailed information about FDA's performance under MDUFA can be found in the 2010 Performance Report to Congress for the Medical Device User Fee Amendments of 2007 at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/MDUFMA/ucm243385.htm.*

With respect to the remainder of your question, the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making engaged in extensive outreach to solicit input from external constituencies and CDRH staff. This includes two public meetings, two public dockets, two town hall meetings, many meetings with individual stakeholders, and an internal CDRH-wide All-Hands meeting. When CDRH released for public comment the two preliminary reports: the *510(k) Working Group Preliminary Report and Recommendations* and the *Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations,* FDA provided copies of the reports and a bicameral briefing to Members of Congress and staff. CDRH also conducted a webinar for the device industry on the recommendations.

In January, 2011, FDA distributed widely its Plan of Action for the recommendations of the working groups to interested stakeholders, including Members of Congress. FDA conducted a media call to which industry, Congressional staff, and other interested stakeholders were invited to listen; another webinar for industry to ask questions; and another bicameral briefing for Congressional staff. FDA continues to respond to requests for briefings from stakeholders.

Seven particularly complex recommendations have been referred to IOM. However, given the concerns raised by external constituencies and CDRH staff about the 510(k) program, such as the flight of companies and jobs overseas, the Agency believes it is important that appropriate actions be taken in the near term to strengthen the program. As we move forward to implement the recommendations, we will continue to engage our stakeholders through public meetings and comment periods for regulations and guidance development. The recommendations of the IOM will probably require additional public vetting before FDA adopts any of them.

Our responses to Questions 4 through 6 are combined.

4. **Biomarkers are a necessary medical breakthrough for those diagnosed with preeclampsia, cancer, heart disease, as well as other diseases and conditions. Unfortunately, patients suffering from these diseases are not able to reap the benefit of having the biomarkers since they can [sic] their physicians in a timely fashion.**

5. **It is my understanding that over the past ten years, the FDA has required much more detailed and extensive clinical information specific to "intended use" of the product. As a result, many companies are launching their biomarkers in Europe 3-5 years before introducing them in the US. In a way, the FDA is regulating the practice of medicine by limiting the use of these biomarkers unnecessarily.**

6. **Will you agree to work with my colleagues and I on the issue of new biomarker development?**

Due to significant differences in regulatory oversight mechanisms of the U.S. and European Union (EU), manufacturers can launch their *in vitro* diagnostic tests for biomarkers in Europe without premarket review under a process called "self-certification." This process amounts to self-regulation, and manufacturers may often launch tests without independent agreement that there is sufficient data to support their intended use. Indeed, the European Commission has recognized that the current oversight system for diagnostics in the EU is not rigorous enough to ensure that patients are getting high-quality diagnostic devices, and has proposed significant changes to the system.

FDA agrees that access to important diagnostic tests is critical for patients. FDA helps patients reap the benefits of these tests by ensuring that tests are accurate and reliable. If they are not, physicians can make misinformed treatment decisions or not treat patients who would have benefited from therapy. In addition, inaccurate test results can lead third-party payers to reimburse for inappropriate therapies or treatments.

Moving forward, FDA would be happy to work with Congress to resolve issues relating to the development and regulatory oversight of in vitro diagnostic tests for biomarkers.

7. What mechanisms do we have to accelerate novel technologies that are needed for patients, but are novel to the FDA in their jurisdiction?

FDA is committed to ensuring that American patients have timely access to important new technologies and next-generation products without compromising device safety. In February 2011, FDA proposed the creation of an Innovation Pathway for novel medical devices. FDA recognizes that transformative devices typically present new scientific and regulatory challenges and the Innovation Pathway supports the development of innovative products by identifying and addressing important scientific questions early to accelerate the development and review of these technologies. In addition, FDA is in the process of establishing networks of external experts to assist the Agency in answering challenging scientific questions, particularly in regard to novel technologies, so that our investigational device exemption and premarket review programs are more timely and efficient.

Under the Innovation Initiative, FDA will also focus on strengthening the U.S. research infrastructure and promoting high-quality regulatory science; and preparing for and responding to transformative innovative technologies and scientific breakthroughs.

8. Countries abroad are tending to turn over technologies at a faster pace in terms of their regulatory oversight. There is a growing tendency by US corporations to do trials abroad first. How can the US remain competitive in this area, while still assuring safety?

Where and when a manufacturer introduces a new medical device is a business decision, influenced by many factors. FDA's mission includes promoting the public health by facilitating medical device innovation generally. Some critics have argued that the speed of the European regulatory approval process is better for industry and patients. However, it is difficult to make direct comparisons between United States and European systems given their fundamental

differences, including, at the most basic level, different approval standards. The EU lacks the requirement in U.S. law that a device be shown to be effective and, therefore, may not require as robust clinical data for higher-risk devices as does the United States. To obtain EU clearance, device manufacturers choose from a list of private companies authorized to perform safety and performance reviews. These are subject to varying degrees of oversight, depending on the country in which they are located. Moreover, unlike the United States, the European system does not have a publicly available, centralized database of premarket review performance data, bases for approval decisions, or adverse event reports. This is, in part, why the European Commission has proposed that the EU regulatory framework be strengthened to better meet European public health expectations and to make European industry more competitive globally.

Moreover, the performance of the U.S. system as compared to the EU system is far better than has been portrayed by critics. According to a recent industry-sponsored study, "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry," most less complex 510(k) devices and roughly half of the more complex 510(k) devices are approved in the United States first. In addition, 95 percent of the over 4,000 medical device applications that FDA reviews each year subject to user fees are reviewed within the goals that were agreed to by industry under MDUFA.

Many of the proposed actions under the Innovation Initiative that we announced in February 2011 will foster innovation for all types of devices, while ensuring that they are safe and effective. The proposals under this initiative include:

- establishing a priority Innovation Pathway for transformative devices that, if adequately resourced, could be expanded to all high-risk devices
- streamlining the *de novo* process for new, innovative, lower-risk devices
- issuing guidance to facilitate the use of clinical data generated outside the United States
- establishing a network of external experts to assist FDA in addressing complex scientific issues
- establishing a voluntary third-party certification program of medical device test centers that would allow for clinical studies to be started earlier in the United States
- developing a core curriculum for device development and assessment to train future device innovators, public-private partnerships, and workshops to promote regulatory science
- enhancing FDA's device horizon scanning efforts, so that FDA is better prepared for new technologies presented for review

In addition, the 25 actions we announced in January 2011 for implementation this year are intended to facilitate innovation for all types of devices by improving the predictability, consistency, and transparency of our premarket review programs.

Through efforts like these, plus a commitment from industry to provide us with better quality data, adhere to Agency advice, and perform better clinical trials, we believe that we can help the United States maintain its position as the global leader in medical device innovation.

9. There are many new technologies that do not fit the current regulations under either devices or biologics, but are combinations of both. Although there is an office

of combination products at the FDA that coordinates these technologies with both branches, the regulations are still specific to each branch, often having to reconcile two sets of regulations that do not necessarily fit the new technology under development. This is causing a delay in the approval of these new device-biologic combinations. How does the FDA plan to address these issues?

The combination products program cuts across drugs, devices and biologics. We will submit this response under separate cover.

The Honorable Ed Whitfield

1. What is FDA doing to help address the public health burden of diabetes in terms of technology development and approval for patients?

FDA has addressed this public health need by increasing transparency, developing new guidance/standards, and increasing public discourse. FDA recently released a document entitled "Development of an Artificial Pancreas for the treatment of Diabetes Mellitus," which outlines FDA's innovative role in regulating these novel device systems. FDA has also developed documentation for researchers and industry that outlines critical information to gain approval for clinical studies for the artificial pancreas system.

For other diabetes devices, FDA has recently published an infusion pump guidance that outlines a new method for ensuring these devices are designed and tested safely prior to clearance/approval. The Agency has also participated in the development of a Continuous Glucose Monitoring standard (CLSI POCT05-A) and a closed-loop control algorithm standard (ISO 60601-1-10) that outlines performance requirements for these medical devices.

Between 2008 and 2010, the Agency has held six diabetes-related device public meetings. These public meetings addressed various performance concerns regarding blood glucose meters, insulin pumps, and artificial pancreas systems. The Agency is using these public meetings to develop new guidance for glucose monitors and artificial pancreas systems.

2. At what stage is FDA involved in the Artificial Pancreas Project?

Since 2007, FDA has been deeply involved with all stages of the artificial pancreas system, fostering collaboration, developing tools to aid researchers, and conducting rapid-response Investigational Device Exemption reviews. In 2008, FDA co-sponsored an Artificial Pancreas Workshop in collaboration with the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation, at which world renowned clinicians and scientists shared information on clinical studies and the challenges in bringing this device system to market.

Again in collaboration with NIH, FDA convened a public workshop in 2010 to discuss the challenges in developing a device system using existing technology and clinical expectations for real-life applications, and to gain feedback on outpatient clinical endpoints for safety and

effectiveness. In 2011, FDA will publish guidance that outlines the clinical study design needed for a marketing application.

3. To what extent will you be taking input from outside entities as part of the regulatory process?

FDA is taking extensive input from outside entities in the development of the artificial pancreas. In 2008 and 2010, public workshops provided feedback from industry, academia, and foundations to improve understanding of clinical study designs needed to evaluate safety and effectiveness and lead to the development of draft guidance.

In addition, FDA developed an interactive review process allowing frequent communication between investigators and FDA staff to quickly resolve outstanding clinical issues. An example of this process is the development of an *in silico* model. This tool was a collaborative effort between FDA and an outside developer that used this model to replace animal studies, thereby saving the investigator months, if not years, of animal research. This effort was instrumental for the progress of the artificial pancreas, as it was the first time the Agency approved an artificial pancreas clinical study without supporting animal studies.

The Honorable John Shimkus

1. As part of FDA's review of the 510(k) process, FDA asked a panel of the Institute of Medicine (IOM) to review seven recommendations the agency viewed as "controversial." The seven recommendations are the following: consolidating the terms "indication for use" and "intended use"; expanding FDA's authority so it can consider off-label use when determining the intended use of a device; issuing guidance on when a device should no longer be available for use as a predicate; clarifying rescission authority; requiring manufacturers to keep one unit of a device available; creating a "Class IIb"; and requiring postmarket surveillance studies as a condition of clearance for certain devices. Similar to the request we made in the letter of October 12, 2010, please provide an analysis of the economic impact of these seven recommendations on the American medical device industry. Further, please explain how FDA intends to take this economic impact into account in its decision on whether to move forward with these seven recommendations.

In your letter of October 12, 2010, you requested that FDA provide the Committee with an analysis of the economic impact of the recommendations on the domestic medical device industry. We are still in the process of determining which recommendations to adopt and are awaiting input from the IOM on these recommendations. We would like to assure you that, as required, economic analyses will be undertaken during the rulemaking process for those

proposals FDA intends to implement by regulation.[5]

2. With respect to those seven "controversial" recommendations and their referral to the IOM panel, I understand there are serious questions as to the composition and expertise of that panel. Please answer the following questions:

a) Does the panel have any inventors and innovators?

Yes. Lazar Greenfield is the inventor of the Greenfield vena cava filter for protection against pulmonary embolism. Gary Dorfman holds several patents related to medical devices.

b) Does the panel have any biomedical engineers or technical experts?

Yes. Yusuf Khan holds a Ph.D. in biomedical engineering. It is not clear to us what is meant by "technical expert," but nine of the 12 committee members have scientific/medical expertise (David Challoner, Gary Dorfman, Lazar Greenfield, Steve Gutman, Yusuf Khan, David Korn, Elizabeth Paxton, Shari Lawrence Pfleeger, and Kathy Zoon). In addition, Barbara Evans, a professor of law at the University of Houston Law Center, holds a bachelor's degree in electrical engineering.

c) Does the panel have any entrepreneurs, investment experts or venture capital experts?

No member of the committee is an entrepreneur or an investment capitalist. Individuals associated with a business venture related to medical devices would be considered to have a conflict of interest and would not be eligible to serve on the committee, consistent with IOM policy.

d) Does the panel have any patients or patient groups who are in need of products currently under the 510(k) system?

No member of the committee is employed by or otherwise works with a patient advocacy group related to medical devices. IOM committees do not typically include representatives of advocacy groups with missions related to the study topic. Such individuals generally have a

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[5] Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) require analyses of the economic impact of regulations. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

conflict of interest and would not be eligible to serve on the committee. The committee obtained input from advocacy groups (and other stakeholders) during public meetings. Additionally, individuals and organizations submitted written comments to the committee during the study process.

e) How much has FDA paid IOM to conduct the review?

IOM received $1,310,780 under the study contract.

f) Is the IOM panel looking at issues outside of the seven recommendations? If so, what are those issues?

IOM's 510(k) study statement of task is identified on the IOM project's website and was available in hard copy at all public meetings of the IOM's 510(k) committee. The statement of task was developed by FDA. The statement reads:

> The committee will assess whether the 510(k) clearance process sufficiently protects patients and promotes public health. Specifically, the IOM committee will answer two principal questions:
>
> 1. Does the current 510(k) process optimally protect patients and promote innovation in support of public health?
>
> 2. If not, what legislative, regulatory, or administrative changes are recommended to optimally achieve the goals of the 510(k) process?

Per the statement of task, the IOM is looking broadly at the 510(k) clearance process. The IOM convened a committee to respond to the statement of task. All aspects of the 510(k) process fall within the bounds of the committee's task. The committee was not given specific direction to review the seven issues identified by FDA at the outset of the process because, at that time, FDA had not yet conducted its assessment and issued its recommendations for public comment. However, that does not mean that the committee will not be addressing those issues in some way.

IOM cannot comment on which, if any, of the seven issues the committee will be addressing in its report. The specifics of the committee's review and its conclusions and recommendations are confidential and have not and will not be shared with FDA until the report is released, consistent with IOM policy.

g) Will the IOM panel have public hearings or receive public input now that the FDA has asked IOM to review those seven recommendations?

Throughout the study, the IOM committee sought and has received a great deal of input from the public. As part of its information-gathering process, the committee held a public session at its first meeting in March, 2010, and two public workshops in June and July 2010. During the workshops, the committee received input from invited speakers and panelists with various

perspectives on the 510(k) process and related components of medical device regulation. Also, the public was invited to provide comments during "open mic" sessions. Members of the public were encouraged to submit written comments. Announcements about how to send comments to the committee were made at the public session and workshops, through the study website, and via the study listserv. The committee received numerous comments from stakeholders. The committee also reviewed the FDA's dockets related to its own internal evaluation of the 510(k) clearance process. Additional public meetings are not planned.

h) Would you please describe in detail the types of communications that FDA has had with this IOM panel, including what was discussed and who was involved in those discussions?

FDA's contract with IOM began on September 20, 2009. IOM staff met with FDA officials on November 24, 2009, to discuss the task order and the scope of the study, and to introduce team members. IOM staff contacted FDA staff a number of times during the study process to request information. All information provided by FDA to the committee has been deposited in the Academies' public access file for this study. The only interaction between the IOM's 510(k) committee and FDA occurred during public meetings.

FDA also contacted IOM for assistance in answering questions from Members of Congress about the scope and methodology of the study.

i) Have there been any limitations placed on interaction between FDA and the panel members?

IOM procedures dictate that panel members are prohibited from communicating with subjects that are currently under review by IOM panels. Therefore, the only interaction between the IOM's 510(k) committee and FDA was during public meetings.

j) What process and timeline will FDA follow once the IOM panel releases its report? Please describe FDA's process and timeline as it pertains to developing and announcing a final decision on the items referred to IOM.

FDA will determine the process it will use after receiving the IOM report, because the process could vary, depending on the recommendations made by the IOM Committee. The type of process adopted by the Agency would affect the time frame for completing our review. For example, FDA might seek additional public input on recommendations which would have a significant impact on regulated industry; or, FDA might first engage with Congress if the IOM Committee recommended new authorities not previously proposed by the Agency.

The Honorable Tim Murphy

1. In your testimony you claimed about workplace drug tests that "If they're not used right then people who actually should get treatment get missed. People who may

have an addiction get missed." The FDA seeks to assert jurisdiction over these tests by defining them as in-vitro diagnostic devices. The statute that determines FDA jurisdiction defines such devices as "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals." 21 USC 321(h). Your claim of jurisdiction may arguably apply to medical treatment for addiction but if a test is used solely for a workplace use such as a pre-employment test where there is no medical treatment provided or offered, how does your claim of jurisdiction apply?

Under section 201(h) of the FD&C Act, the term "device" is defined, in relevant part, as an "instrument, apparatus . . . or related article . . . which is . . . intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, . . . or [is] intended to affect the structure or any function of the body" (21 *United States Code* (U.S.C.) § 321(h)). Drugs-of-abuse tests are devices within the meaning of the Act for a number of reasons, including those discussed below.

In detecting whether drugs of abuse are being used or have been used by a person, drugs-of-abuse tests are diagnosing a condition, and drug use may be an indicator of other conditions or disease, such as drug addiction. The Act does not limit the device definition to products intended for use only in a medical context. "The plain meaning of 'diagnosis' disregards context and bears no connection to medical treatment" (9 *United States v. An Undetermined Number of Unlabeled Cases,* 21 F. 3d 1026, 1028 (10th Cir. 1994) (holding that specimen collection containers used in collecting samples to assess the presence of HIV antibodies solely for insurance assessment purposes are "devices" under the Act and subject to FDA regulation, and stating "the fact that insurance companies rather than health professionals considered [the test results] to make business rather than medical decisions does not erase the diagnostic character of . . . the [product's] use")). Indeed, FDA's classification regulation for over-the-counter (OTC) test sample collection systems for drugs-of-abuse testing, 21 CFR § 864.3260, expressly applies to devices used in a non-medical context, i.e., "outside of a medical setting and not on order of a health care professional (e.g., in the home, insurance, sports, or workplace setting)" (21 CFR § 864.3260; 65 *Federal Register* (FR) 18230, 18230 (April 7, 2000)). In this preamble, FDA expressly rejected a comment suggesting that FDA exercise enforcement discretion with respect to drugs-of-abuse tests for workplace use because FDA explained that the workplace setting, like the home, insurance and sports settings—and unlike the law enforcement setting—implicates concerns about "consumer use and quality. . . including concerns about sample integrity and test accuracy" (65 FR at 18230). FDA further stated that it would "continue to exercise its enforcement discretion with respect to the use of these products [drugs of abuse test sample collection systems] in the law enforcement setting because there are protections to ensure sample integrity and test accuracy that are not generally available in the home, workplace, insurance and sports settings," such as the rules of evidence and the representation of the accused through the judicial process.

FDA review also provides an independent assessment of the performance of the test to ensure that users, such as employers, have access to a test that is accurate and reliable and ensures that the information in the labeling is truthful and that the labeling conveys information that would be important to the user (e.g., contains instructions for confirmation, etc.). To obtain clearance, a manufacturer must demonstrate that the risk of false results is adequately mitigated. There is

generally more tolerance for false positive results as they are generally confirmed; too many false negative results would not be acceptable. Thus, FDA review of drugs-of-abuse tests is necessary to ensure that these tests are sufficiently accurate and reliable. Further, other federal agencies rely on FDA review of drugs-of-abuse tests with respect to the drug testing programs that they administer. For example, the Substance Abuse and Mental Health Services Administration (SAMHSA) requires that the initial drug test "be approved, cleared, or otherwise recognized by FDA as accurate and reliable for the testing of a specimen for identifying drugs of abuse or their metabolites" ((73 FR 71858, 71892 & 71897) (Nov. 25, 2008) (SAMHSA's revised mandatory guidelines for federal workplace drug testing programs)).

2. **Is it your assertion that it is the responsibility of employers to provide for diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease of every employee based on a screening test? If this is an employer's obligation to cure, mitigate or treat the employee's disease, then each and every company that uses these point of care devices would have to have a medical doctor or drug counselor on staff at all times or on retainer. Is that a feasible option?**

For several decades the standard for drugs-of-abuse detection programs at the workplace has been set by federal agencies that run programs in the federal government, such as SAMHSA, the Department of Transportation, and the Nuclear Regulatory Commission. Those programs, and private industry programs modeled after them, typically have a Medical Review Officer to oversee the program. It is true that many private companies, particularly small businesses, may not have medical personnel to oversee their programs. In these cases, companies may use drug screening tests that are intended for OTC use.

3. **In your testimony, you note that "they pose a risk" or "they get false results" and they wind up "losing their employment". You also stated that your main claim to jurisdiction is that you "have regulated because of the safety concerns that occur when those tests are inaccurate." Your concern about workplace safety is laudable, but how does the above definition of a medical device give the FDA jurisdiction over workplace safety? Moreover, if someone was denied employment because of a test result, would this not be more appropriately addressed within the Department of Labor?**

Please see our response to Question 1 above for discussion of jurisdiction over drug tests used in workplace settings.

FDA review of the labeling and the data relied on to support the claims for drug testing devices provides assurance to employers that the test they choose is sufficiently accurate, that the information in the labeling, including any performance claims, is truthful and not misleading, and that the intended user is able to understand the instructions for use. FDA review also ensures that the labeling clearly states that test results are preliminary, and that a positive result should be confirmed with another testing method. Such information is particularly important when medical professionals are not involved in the testing, as may be the case for smaller companies. Without confirmation, false positive results may result in inappropriate clinical intervention, inappropriate termination, or rejection of otherwise eligible job candidates.

We agree that FDA would not play a role in adjudicating denials of employment based on test results. However, FDA's role in ensuring that tests are sufficiently accurate is especially important to employers to ensure that they do not miss identifying someone who uses or abuses drugs. FDA review ensures that the tests are sufficiently accurate to detect whether a drug is present. Inaccurate tests may increase risk to the public.

4. **In your testimony, you explain that a drug test is used to diagnose addiction (see question 1). How does a screening drug test diagnose addiction? Doesn't there have to be additional information gathered to diagnose an addiction?**

Articles that aid in the detection and screening of a condition or disease are considered devices under the Act (See, *e.g., United States v. 25 Cases . . . Sensor Pad for Breast Self-Examination,* 942 F.2d 1179 (7th Cir. 1991) (holding that a pad used as an aid in the detection and screening of breast cancer is a "device" within the meaning of the Act)). Many laboratory tests are used in conjunction with other information (e.g., behavior, appearance, other clinical factors) to determine whether someone has a particular disease or condition. For this reason, we clear and approve many diagnostic tests that are intended to be used as an "aid in diagnosis" of the indicated condition or disease. Drug screening tests that detect the presence (or absence) of a drug in a clinical sample are one part of the evaluation when someone is being evaluated for addiction.

5. **The manufacturers of the tests point out that the non-medical uses of drug tests in the workplace are:**

   a. To promote an orderly work environment and deter drug use.
   b. To provide a cost effective method to reduce employer costs associated with drug abuse.
   c. To discourage illegal or immoral conduct by employees.
   d. To promote workplace safety.

   If manufacturers added a disclaimer to their products stating that the test kit was not to be used to make any medical decisions, would that address your concerns? It is my understanding that the tests are already clearly marked and marketed as preliminary screens that require confirmation of any positives before any action should be taken.

A disclaimer would not address the risks related to potentially inaccurate tests, particularly those that may generate an unacceptably high number of false negative test results.

Although confirmation testing could be performed for all screening results, in reality, only positive screening results are sent for confirmatory testing. Even the Federal Drug-Free Workplace Program that is run by SAMHSA and the drug screening programs run by the Department of Defense (two of the most comprehensive programs in the country) do not require confirmatory testing for negative screening results. Therefore, when a false negative screening result is generated (i.e., the test does not detect a drug in the sample when present), that result is relied on and drug use or abuse is not detected.

Detection of drug use is the reason that employers participate in drug-screening programs. False negative results are particularly serious where an immediate result is needed to determine if it is safe to allow a worker to perform his or her job (e.g., heavy machine operators, truck drivers, etc.). False negative results may also increase risk to the public, for example, when such a result is relied on to allow a pilot to perform his duties, putting himself, the passengers, and others at undue risk.

6. You stated that "We have one that is point-of-care test for saliva that actually is pretty good." How did FDA determine the test to be "pretty good"?

FDA has cleared two point-of-care tests (also called point-of-collection or on-site tests) for saliva. The tests, LifePoint Inc.'s IMPACT Test System and OraSure Technologies' UPlink Test System, were cleared based on the information, data and claims provided by the test manufacturers in their premarket notification submission to FDA.

The review standard used was the FDA clearance standard under 510(k) of "substantial equivalence" to other similar marketed saliva drug test devices. The tests were reviewed to evaluate whether they could detect the presence or absence of drug in a saliva sample with appropriate accuracy, and whether the labeling includes information that would enable a user to perform the test properly and correctly interpret the test result. The LifePoint IMPACT Test System was cleared for OTC use and may also be used in employment settings without medical personnel.

7. You stated that "The rest that have come through are actually very poor." Did you review analytical or clinical data from these manufacturers before deciding they were "very poor"?

FDA has reviewed data for certain saliva drug tests, the performance of which has been quite poor. We review data on analytical validation (such as accuracy and repeatability) typically in spiked or diluted samples, and for clinical validity by assessing data to determine whether the device can give an accurate result in natural samples. The most common issue for poor-performing saliva drug tests is the high rate of false negatives.

There are some significant scientific challenges to overcome when developing saliva test devices. For example, there is a general tendency for drugs present in the saliva sample to "stick" to the sides of the saliva collection cup (sometimes as much as 90 percent). When this happens, the sample tested by the device no longer contains sufficient drug to be detected, and a negative result is generated even though there was drug in the original sample.

Did you receive any information on these tests from sources other than the manufacturers? If so, please identify the sources and provide the information given to the FDA.

The data FDA has reviewed were submitted by test manufacturers to support the clearance of their new devices. We have not received data or information on specific tests from sources other than the manufacturers of those tests, although the scientific challenges are widely known in the

drug-testing community and have been discussed both in the literature and at scientific and policy meetings.

8. What FDA guidelines or rules or processes did you use in evaluating these tests?

Drug tests, including saliva drug tests, are cleared based on the information, data, and claims provided by the test manufacturers in their premarket notification submissions to FDA. The review standard that is used is the FDA clearance standard of "substantial equivalence" to other similar drug test devices that are on the market. FDA has cleared approximately 40 saliva drug tests to date. You may view the guidance document, Premarket Submissions and Labeling Recommendations for Drugs of Abuse Screening Tests - Draft Guidance for Industry and FDA Staff, at *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070612.htm.*

9. When asked about the FDA threatening to shut down operations of American manufacturers making the tests, but not of foreign-based manufacturers, you answered that "We've actually been sending warning letters to a variety of different companies." Please list the companies you have sent warning letters to and the dates you sent such letters and please provide the warning letters.

Since 2009, FDA has sent Warning Letters to several drugs-of-abuse manufacturing firms. These recent warning letters were sent to the following companies:

- Express Diagnostics International[6]
- W.H.P.M., Inc.[7]
- American Bio Medica Corporation.[8]
- Branan Medical Corporation[9]

In addition, in 2010, FDA contacted all companies, foreign and domestic, of which the Agency was aware were marketing saliva drug test devices without FDA clearance. FDA intends to continue to make every effort to ensure fair and equal treatment of companies in this area and provide them with a reasonable opportunity to come into compliance with applicable regulations.

10. When you were asked about if you had responded to the September 2010 request from American based manufacturers for proper written guidance, you stated: "Well, we did one better. We've actually been talking with them and walking them through what exactly they actually need to do, because we have experience with these kinds of tests." It is my understanding that the FDA has not yet provided written guidance to industry. Can you provide an answer as to when you expect to provide guidance for saliva testing kits?

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[6] *Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm132587.htm*
[7] *Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm132583.htm*
[8] *Available at: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm198318.htm*
[9] Available at: *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070612.htm*

FDA has published draft guidance for drug tests, *Premarket Submissions and Labeling Recommendations for Drugs of Abuse Screening Tests - Draft Guidance for Industry and FDA Staff.*[10] This guidance addresses all types of drug tests, including tests for laboratory use, home use, and workplace use. In addition, the guidance also applies to drug tests for all sample types (urine, saliva, hair, etc.). This guidance document is regularly used by drug-test manufacturers to guide their development of data and information, including the design of studies, needed to support FDA clearance for their tests. The draft guidance provides high level recommendations on study design, general considerations, and labeling.

In addition, FDA posts summaries of all past clearance decisions for diagnostic tests on its website. These decision summaries contain detailed descriptions of the studies performed and the data used to support clearance for each device. These are often used by manufacturers as a resource to design their own studies and determine the appropriate level of accuracy for their tests.

Where companies would like specific guidance on their particular test or technology, FDA also has a mechanism to meet interactively with individual companies regarding their specific tests. Through this mechanism, the Agency provides direct feedback on questions and study proposals to help guide individual companies with their test development and validation efforts.

These resources have been proactively provided to manufacturers in the drug testing community, and they have been very effective for those companies that have chosen to use them.

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[10] Available at:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070612.htm

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUN 09 2011

Dear Mr. Chairman:

Thank you for your letter of March 17, 2011, to Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health (CDRH or the Center) at the Food and Drug Administration (FDA or the Agency), regarding questions submitted for the record by Members of the Committee. These questions are in follow up to the Committee's February 17, 2011, hearing entitled "Impact of Medical Device Regulation on Jobs and Patients."

By letter dated April 12, 2011, FDA provided responses to all questions submitted for the record, with the exception of Question 9 from Representative Michael C. Burgess. This supplemental response addresses Question 9.

Thank you again for contacting us concerning this matter. If you have further questions, please let us know.

Sincerely,

Michael Mital

for Jeanne Ireland
Assistant Commissioner
for Legislation

The Honorable Michael C. Burgess

9. **There are many new technologies that do not fit the current regulations under either devices or biologics, but are combinations of both. Although there is an office of combination products at the FDA that coordinates these technologies with both branches, the regulations are still specific to each branch, often having to reconcile two sets of regulations that do not necessarily fit the new technology under development. This is causing a delay in the approval of these new device-biologic combinations. How does the FDA plan to address these issues?**

The Federal Food, Drug, and Cosmetic Act and the Public Health Service Act provide approval standards for drugs, devices, and biological products. The Agency regulates combination products in accordance with these statutory standards. These statutes do not provide a separate standard for the approval of combination products.

Combination products, such as the device-biological product combination products to which you refer, are often complex in both their composition and interactions with the body. As a result, the time needed to review them can be longer and the resources required more extensive than for less complex products.

By statute, the "lead" Center for reviewing a combination product is determined based on which constituent part (drug, device, biological product) of the combination product provides the "primary mode of action" or "PMOA" (FDA regulations define PMOA to be the single mode of action of the combination product that is expected to make the greatest contribution to the overall intended therapeutic effects of the product). For example, CDER would have the lead for a pre-filled syringe because the drug constituent part provides the PMOA; whereas, CDRH would have the lead for a drug-eluting stent because the device constituent part, which keeps the blood vessel open, provides the PMOA. Typically, the review of a combination product is a collaborative process in which the lead Center consults with the Center(s) with expertise for the other type of constituent part(s) to ensure appropriate consideration for all relevant review issues for the product. As the number of combination product submissions increases, the need for additional resources and expertise will continue to grow.

While FDA must, of course, work within the current statutory framework, we seek to make the regulatory process for combination products as transparent and streamlined as possible, consistent with ensuring product safety and effectiveness. As FDA gains experience, we are actively engaged in modifying and developing internal procedures and developing guidance and rules to clarify regulatory requirements for these products. FDA proactively seeks stakeholder input regarding what issues would be most helpful to address through such efforts.

In light of stakeholder input, we have issued guidance of general application for combination products — for example, regarding early product development questions—and are currently developing guidance on topics including clinical and technical development considerations and post-approval changes to combination products, with the goal of publishing drafts this year. Similarly, we have developed guidance for specific types of combination products that are widely marketed or have repeatedly raised regulatory questions, such as auto-injectors and

drug-eluting stents. These and other FDA guidance documents pertaining to combination products are available on the Agency's web site at *http://www.fda.gov/CombinationProducts /Guidance RegulatoryInformation/ucm109110.htm.*

We continue to consider what additional measures we can take to enable more efficient review of combination products, such as creating cross-Center review teams, issuing additional guidance, and drafting new regulations addressing combination products.

Does the FDA plan to create a new C.F.R. for these new technologies?

We are not planning to create a new regulation at the present time regarding review of combination products, although we are in the process of finalizing two rules concerning current Good Manufacturing Practice and adverse event reporting for combination products. We also continue to seek stakeholder input as to what issues would benefit from greater clarity through guidance or rulemaking.

March 27, 2011

Honorable Joseph R. Pitts
Chairman, Health Subcommittee
House of Representatives
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Honorable Chairman Pitts,

Thank you for your follow-up questions to my testimony February 17th, 2011 at the hearing entitled "Impact of Medical Device Regulation on Jobs and Patients." My responses are below as per the format requested:

1. **Your 2010 study analyzed FDA's impact on medical technology innovation. You highlighted the lag between the availability in products between the EU and the US. You also highlighted the increased time and cost required to bring a product to patients and the overall lack of predictability and efficiency in the U.S. regulatory process that is making it difficult for companies to get life-changing medical products into the hands of clinicians and patients.**

    a. **What is causing these problems at FDA?**

Given that the laws governing FDA have not changed since 2007 and the difficultly navigating FDA has increased over the past few years, I believe the problems have arisen as a result of a response from FDA officials to inaccurate claims that FDA was not doing a good enough job protecting patients. These criticisms have come from multiple sources, but the most influential have been the letter from the "concerned scientists" at FDA and also the often misinformed coverage of FDA issues in the media. In contrast to these perspectives, Professor Ralph Hall's research confirms FDA's stellar safety record, suggesting that much of what makes headlines on this topic is anecdotal. Further, an internal investigation conducted in response to the letter from the "concerned scientists" found no evidence of wrong doing. Unfortunately, however, these two forces have fundamentally changed the mindset at the FDA and the agency has

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become more risk-averse over this time period. When such an environment exists, all too often the best decision for a team at FDA reviewing a device is to make no decision at all and find reasons for rejecting or delaying ultimate approval or clearance. Also, due to internal upheaval and unrest within the agency related to the allegations made by the "concerned scientists", there is a prevailing fear among reviewers and managers of being perceived as "giving industry a pass." As a result, they sometimes seem to be using low-probability scenarios and concerns, not necessarily backed by scientific evidence, to present hurdles for reviews. Driven by concerns over conflicts of interest, the spirit of collaboration with industry and other stakeholders has been substantially damaged. Lastly, there is a wide variety of approaches review teams take when evaluating an application because of a lack of standardization. As result, the reviews can vary widely in their timeliness and reasonableness, resulting in a substantial lack of predictability and transparency.

b. If we continue on the current trajectory, where do you see medical innovation in 10 years? What would be the impact on American patients? What would be the impact on American jobs?

The urgency to address our current regulatory challenges, is important because our competitors in Europe, Latin America, India, China and other emerging markets are already watching us fall behind and many are positioning themselves very well to reap the rewards. As we have seen in other industries that have left the US, when conditions reach a breaking point, the shift can happen dramatically and irreversibly. We are already beginning to see the slow migration of manufacturing jobs and investments being made overseas in this innovative sector. My concern is not only that medical innovations will decrease overall, but that they will be developed and nurtured outside of the United States. Having worked in this industry for over 20 years, I know the passion and entrepreneurial spirit of my colleages, but without a predictable and reasonable regulatory framework, their ideas and innovations will be developed elsewhere. Worse yet, we will see the best and brightest minds that have historically sought out the medical technology sector shift towards other professional pursuits or leave the country. This will have a devastating impact on patient care and job creation. American patients will wait longer for access to medical technologies, and the innovations that we have grown accustomed to will thrive in other nations first. The impact on job creation to the medical technology sector would be devastating, and my greater fear is that the jobs that are lost will never come back. Lastly, to have fundamental life-saving technologies based and primarily developed overseas is also a substantial national security concern.

2. **In addition to your study, I understand that PwC and California Healthcare Institute recently released studies that confirmed that problems at FDA are costing our nation jobs and hurting our nation's patients. Would you describe these studies, their findings, and what they indicate about the future of American device firms and jobs? Also, what will be the impact on patients?**

PricewaterhouseCoopers LLP (PwC) revealed its Innovation Scorecard on medical technology, and the message was dire. Their study looked at medical technology innovation in nine countries: Brazil, China, France, Germany, India, Israel, Japan, United Kingdom, and the United States.

Quoting the key findings that they identified:

- "The medical technology innovation ecosystem, long centered in the United States, is moving offshore. Innovators are going outside the United States to seek clinical data, new-product registration, and first revenue.
- US consumers aren't always the first to benefit from medical technology and could eventually be last. Innovators already are going first to market in Europe and, by 2020, likely will move into emerging countries next.
- The nature of innovation is changing as developing nations become the leading markets for smaller, faster, more affordable devices that enable delivery of care anywhere at lower cost."

PwC looked at several factors in innovative nations, including the availability of investment resources and efficiency of regulatory systems. The study clearly showed that American innovators are seeking clinical data and revenue outside the US first. While much of this innovation is first accessible to European patients, the study notes that, by 2020, it is likely that other nations, including Brazil, India and China, will benefit from America's regulatory challenges.

A recent study conducted by the Boston Consulting Group (BCG) answered the question whether devices approved in Europe were more or less safe than those in the United States. The BCG report examined the rate of safety recalls for medical devices in Europe from 2005 to 2009 and compared them with the level of similar recalls in the US. It found that there is little to no difference between average recall rates in the US and the EU. Essentially, American patients and workers are unfortunately not getting any incremental safety benefit from the added costs and delays of our current system.

Nobody opposes the FDA asking for clinical data when the circumstances warrant it. In fact, the agency currently has the authority to demand data whenever it deems it necessary. The problem for medical technology innovators arises when the requirements change at the FDA without transparency or justification. This uncertainty is harmful to innovation, job creation and patient care because it stymies future investment in medical technologies.

PwC's report is very frank in its assessment: if these indicators do not change direction, the United States' leadership position in medical technology innovation will continue to erode, and we will find ourselves trailing our competition. This is a situation where American patients and entrepreneurs cannot reap the rewards of homegrown innovation. As the BCG study makes clear, there is no statistical basis for the "device lag" that is occuring in the United States.

Regarding its impact on American patients, this will contribute to the "device lag" where we are waiting months, sometimes years, after our neighbors in other countries have access to the latest and best medical technologies. Given that there is no evidence of a safety benefit from this delay, the net impact will be that American patients will be essentially getting yesterday's technologies delivered at a higher cost.

3. **Would you describe the types of devices that are available in Europe and not available in the United States? What type of impact does this have on American patients?**

There are numerous devices that are available in Europe, years before they will ever be available in the United States. One example which has resulted in tens of thousands of patients outside the United States gaining access to lifesaving devices is catheter-delivered replacement heart valves. These devices are currently being used in Germany and many other European nations, and have been proven to have a substantial outcome benefit for properly selected patients. Studies have shown that very sick patients with catheter-delivered valves were significantly less likely to die after a year than people who were treated medically but didn't get a new valve. In fact, the data was so compelling that companies are reassessing how to proceed with clinical studies as the positive data is so overwhelming that it borders on unethical to not provide every patient in a study with these devices.

Tragically, these are not available in the United States, and it could potentially not be available for be several years. This is probably one of the most severe examples where American patients wait at risk for access to American innovation while others outside the US benefit.

The New York Times recently reported about a patient, Marti Conger, who suffered from debiltating back pain and was thrilled to identify a technolgy, with the assistance of her physician, to address her ailment. The device she wanted was developed by a company 40 miles from where she lived and had a solid 5 year track record of treating thousands of patients. However, the product is not approved in the US, so the patient needed to save up tens of thousands of dollars to fly to Europe and get the procedure done. It was reported that she is now feeling great, but Americans should not need to travel thousands of miles and pay tens of thousands of dollars for therapies that were developed in our country.

While it is clearly an individuals choice to travel abroad for access to care not available in the United States, the overwhelming majority of Americans do not have the resources to do so. As Marti's storymakes profoundly clear, these are not easy decisions. Patients are going bankrupt trying to access devices and technologies that can improve – if not save – their lives. This doesn't even take into consideration the countless patients who have no choice but to remain here without access to these therapies, despite the fact they are in wide use outside the United States.

While we've discussed above heart and spine devices, I am aware of devices that address clinical issues in nearly every organ system that are available outside the US and have still not been granted approvals here.

4. **Based on FDA data, the average 510(k) decision time has risen 20 percent from 97 days in 2002 to 116 days in 2008. Why has the number of FDA review days increased? Is there a similar problem with PMA review times?**

Yes, both the 510(k) and PMA average review times have gotten dramatically worse over the past few years. Given that the number of submissions has been relatively flat, the delays can not be attribited to increased workload. I suspect that the delays are driven by the risk-adversion mentioned above. "New science" or poor quality submissions have been suggested by FDA to be the cause, but I truly do not believe those are major factors. In a setting where the rules continue to change and the mileposts continue to be moved out, FDA's view of quality is likely based on a constantly moving standard which is near impossible to predict or plan for.

5. **As you know, FDA requires clinical trials for certain devices in order to obtain clearance or approval. FDA is required by statute to approve an Investigational Device Exemption (IDE) to allow the study of investigational device in humans in clinical trials. According to most observers, the IDE process is broken and needs to be fixed due to a lack of predictability and consistency in how FDA reviews and approves IDE applications. The result is prolonged reviews and unreasonable requests from FDA concerning clinical trial design. Small start-up companies have had to close their doors because of a lack of funds resulting from the unreasonable amount of time spent responding to FDA requests without obtaining final IDE approval to begin their clinical studies. Because of the broken IDE process, more and more U.S. device manufacturers are conducting their trials overseas first. Are you aware of these trends? How long should it take FDA to approve these IDEs? How long is it actually taking? Do you have any suggestions of how FDA can improve the IDE process to prevent companies from failing or moving jobs or clinical trials overseas?**

I am well aware of the concerns relating to IDEs, both through the responses to the survey I conducted and with the companies I am incubating. FDA's charge regulating medical devices is to ensure a "resonable assurance of saftey and effectiveness". However, it appears that FDA is substituting "absolute" instead of "reasonable" in many cases. It has appeared to me and my colleagues that many reviewers are asking for data that goes far beyond the traditional check for safety issues before clearing a device for study, and are now challenging the companies to produce data typically only required prior to approval. Another trend many of us are experiencing is that review teams can get caught up in theoretical concerns which have little or no scientific basis, but rather repesent the concerns of one reviewer. Given the difficult position managers were put in by the letter of the "concerned scientists," managers in these situations have a hard time over-ruling or dismissing these issues. While FDA is required to respond to IDEs within a designated time period, often the responses arrive on the companies fax machine on the last day on the last hour, and when this happens the response is often negative with FDA asking for additional information. This is the way that the proposed timelines for turning around an IDE are rendered useless. As a result of these frustrating delays, companies are choosing to develop their products and conduct clinical trials overseas where the requirements are straighforward, transparent and reasonable, using globaly accepted standards to guide the process. I would strongly recommend that FDA adopt these international standards to improve their process and bring clinical trials back to the US. Further, I would propose that for FDA to move away from a historical or international standard, the FDA review team should be required to make a valid, reasonable case based on existing scientific evidence, rather than use theoretical concerns to delay IDEs.

6. **How does the EU device regulatory system compare to the U.S.?**
    a. **Are the EU regulations more predictable and certain? Why does that matter to device firms?**

I believe the regulatory pathway in Europe is currently more predictable and transparent than the United States. When you begin the process for having a device reviewed, there are very clear expectations, endpoints and you know what data a reviewer is looking for. Medical device innovators are then able to proceed with the confidence that if they meet the goals that have been established, they will gain access to the market. This increases investment, leading to job creation, and upon a successful review, new improvements to patient care.

Predictability and certainty in the regulatory framework is crucial to device firms for several reasons. First, in order to build an effective clinical trial, business model, etc., one must clearly understand what the expectations are to map out the path forward. This "map" dictates funding, research and development, job creation, everything that goes into growing a medical device company. If there is no predicatbility, investors become hesitant, job creators unwilling to hire, and devices and technologies fail to gain access to the market. This failure is not due to concerns with their safety and effectiveness, but the economic and regulatory realities created by moving goalposts.

    b. **Is the EU approval process more lenient? What is the approval standard?**

The European approval process is not more lenient, it is simply more predictable, transparent and reasonable. The approvable standard in Europe is often laid out very clearly through pre-existing documentation, or through a binding conversation with the notified body. Unlike the process in the US where review teams often try to tweak multiple variables, resulting in a lengthy difficult negotiation over endpoints or statistical methodology, the officials at the EU generally respect traditional academic standards for the particular field of investigation and rely more heavily on expert physician or scientist input and guidance than their own theoretical concerns. Thus, if one conducts the generally acceptable pre-clinical and clinical testing for a new technology and the results are successful, the technology is usually granted access to the market.

c. Does the EU have more safety problems?

There is absolutely no data that I am aware of that supports the claim that the European regulatory pathway has more safety problems. As noted above in Question #2, the BCG study was unequivocal in showing that there is no difference in European and American recall rates, and thus the European regulatory pathway appears to be equivalent in safety to the US.

d. Are devices less effective in the EU compared to the U.S.?

I am not aware of any studies or data that show devices used in Europe are less effective than those in the United States. In fact, many devices first approved by CE ultimately are approved in the US as well after the delay.

7. **During the hearing, with respect to evidence showing that less than 0.5% of 510(k) devices have been subject to a Class I recall, one of the witnesses, Dr. Steven Nissen, twice asked the question that if an airplane pilot announced that there was a 99.5% chance of a flight reaching its destination safely, would people take the flight. This question seems to suggest that, short of ensuring that a device is certain to be 100% safe, it should not be approved for use in patients. Is this approach or mentality driving FDA decisions concerning the approval of medical devices?**

I truly hope not, but it is persectives like this that have poisoned the debate over this issue and distorted the public's view of what can reasonably be expected from medicine and surgery. Today, I know of no medical procedure or device that would meet this 100% standard. As I mentioned in answer to question #1, it is clear that this expectation has driven the FDA to become much more risk-adverse over the past years. As a physician-inventor, my primary responsibility and focus is always toward the patient. My colleagues and I work tirelessly to deliver the best products and technologies while minimizing the risks that are always present. While we all strive to reduce the likelihood of adverse outcomes, the reality is that the delivery and practice of medicine involves human interaction, with limitless scenarios and factors that makes no patient identical. Setting a standard that the only acceptable level of risk is zero, and that a 99.6% success rate is considered a failure, only sets up patients, innovators and entrepreneurs for lost opportunities, and will clearly harm the delivery of care. In the end, it comes down to a reasonable balance of the risks and benefits, and this decision is best made between a doctor and their patient with full acknowledgement of the uncertainties that exist.

Thank you again for giving me an opportunity to contribute to this important discussion. If you or the Committee members have any further questions, I remain open to addressing them to the best of my ability. I am deeply appreciative of the focus the Committee has placed on this issue and thank you for the important work you are doing to help patients and jobs in America.

Sincerely,

Joshua Makower, M.D.
Chairman, Founder & CEO, ExploraMed Development, LLC
Consulting Professor of Medicine, Stanford University
Venture Partner, New Enterprise Associates

Written Response to Post Hearing Questions Posed by Chairman Pitts
Hearing Title: "Impact of Medical Device Regulation on Jobs and Patients"
Hearing Date: February 17th
Respondent: Mark Deem

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1. **I understand that PwC and California Healthcare Institute recently released studies that confirmed that problems at FDA are costing our nation jobs and hurting our nation's patients. Would you describe these studies, their findings, and what they indicate about the future of American device firms and jobs? Also, what will be the impact on patients?**

   Both the CHI report and the report by Dr. Josh Makower document the dramatic increase in approval and clearance times by the FDA for new medical devices. Across our industry, there is near unanimity that over the last few years, without any change to regulatory legislation, FDA has implemented policies and fostered an environment of risk aversion which has negatively impacted time to market for lifesaving new therapies. In addition to long approval times, there has been a decrease in communication from the agency, a decrease in transparency of the regulatory process, and an increase in consistency.

   The result of these changes has been for entrepreneurs like me to move clinical trials, manufacturing, and some cases our entire companies overseas. This naturally impacts our hiring, moving jobs previously held by Americans overseas. This also has the impact of teaching overseas physicians, engineers and clinical trial professionals the intricacies of medical device startup creation and management. We are already seeing an uptick in startup activity overseas as a result. Places like Israel, Singapore, Taiwan and Europe are actively supporting these efforts by their home-grown entrepreneurs financially and with infrastructure support. We are at the verge of losing our leadership role in what is truly an American grown industry.

   Ultimately, American patients lose. As the reports cited document, there is currently an average of a four year lag between when European patients see new medical device technology and when American patients can benefit from these therapies, more often than not therapies that were invented in their own back yards. Examples include catheter based aortic valve replacement – today 30% of German patients who have aortic valve replacement benefit from this minimally invasive therapy while American patients still have their chests cut open to have a new valve implanted. Artifical spinal disks are in their 4th generation of evolution in Europe today, while American patients have access to 10 year old, first generation technology.

2. **Would you describe the types of devices that are available in Europe and not in the United States? What type of impact does this have on American patients?**

   As mentioned above, there are many technologies which are either not available at all in the United States today, or which are available only their crudest, first generation forms. Two of the most talked about technologies which are available

in Europe but not in the US are catheter based aortic valve replacement and Artifical spinal disks. Again, today 30% of German patients who have aortic valve replacement benefit from this minimally invasive therapy while American patients still have their chests cut open to have a new valve implanted, and artificial spinal disks are in their 4th generation of evolution in Europe today, while American patients have access to 10 year old, first generation technology. At least one of these spinal disk companies is now moving its entire operation overseas.

There are however a number of other therapies which will not reach American patients for years, if ever. A new catheter based therapy developed by Ardian, Inc, and now sold by Medtronic, provides a 30 point drop in blood pressure for patients who have uncontrolled hypertension which cannot be controlled by medication. This dramatic imrovement in hypertension is achieved with a single 30 minute minimally invasive procedure. We know that heart attack, stroke and death are all greatly reduced by controlling hypertension. So thousands of Americans will suffer these conditions which could have been prevented if the US regulatory environment were more efficient and predictable.

Many other examples exist as well. A next generation coronary stent technology developed by a now defunct company named Xtent, Inc. tried for two years to gain approval from the FDA just to START a clincal trial. Because of this delay the company ran out of money and was sold off at pennies on the dollar to a Chinese firm. The technology is now under development and will be available overseas. Therre are no plans to ever introduce the technology in the US. At the time that the company was struggling to get its IDE approved, there was significant data from clinical trials in humans in Europe with up to two year folllwup, demonstratingsafety and effictiveness.

Intrapace, Inc recently announced that it had raised additional venture capital to introduce its obesity technology in Europe, and statedpublicly in the press release that it wold likely never seek US approval.

A minimally invasive therapy for emphysema closed its doors after an extremely poorly run panel review and a series of personnel changes in the agency. That technology was sold for pennies on the dollar and is now available only in Europe.

In the interest of keeping this answer to a reasonable length I will stop here, but there are more examples, and unfortunatly more and more are occurring.

3. **Based on FDA data, the average 510(k) decision time has risen 20 percent from 97 days in 2002 to 116 days in 2008. Can you think of a reason as to why the number of FDA review days has increased?**

The mechanistic reason for this increase is an increase in the rounds of questioning that the FDA submits a company to. The FDA rarely misses its due dates for responding to a filing – and so their self-reported performance statistics look good. In reality, the clock stops every time the FDA writes a letter back to a sponsoring company. They measure time in FDA days, not in real-world calendar days.

The underlying reason that these rounds of questions have increased, resulting in increased clearance times, are multifactorial. A preponderance of junior reviewers with little real world experience, minimal training and in some cases little managerial oversight all contribute to it.

A major factor though is in decrease in risk tolerance within the agency. All physicians know that there are no completely safe therapies. All premarket evaluations and clinical trials evaluations must be based on an appropriate risk:benefit analysis. The agency seems to have shifted over the last couple of years to an extremely conservative nature. In some cases, medical reviewers within the agency contradict the risk:benefit opinions of world renowned experts in a given clinical area to err on the conservative side.

In the evaluation of risk:benefit, reviewers take their lead from Agency management, and to some extent management takes its cue from Congress. Many of the issues related to clarity and approval times can only be solved when Congress gives clear direction to management, and holds management accountable for adjusting its expectations back to a more balanced view.

Congress also needs to understand the impact that it has on the Agency and the perception of what appropriate risk tolerance is. Previous leadership of this subcommittee and of Energy and Commerce helped swing the pendulum towards today's extreme conservatism with its handling of the uproar over the whistleblowers' letter of 2008, and with several instances where agency management was called to testify to defend itself after device failures or recalls. I applaud today's leadership for taking a more balanced view, and I urge this and future leadership to continue to recognize what patients and physicians face every day – there is no benefit without risk.

4. **As you know FDA requires clinical trials for certain devices in order to obtain clearance or approval. FDA is required by statute to approve Investigational Device Exemption (IDE) to allow the study of investigational devices in humans in clinical trials. According to most observers, the IDE process is broken and needs to be fixed due to lack of predictability and consistency in how FDA reviews and approves IDE applications. The result is prolonged reviews and unreasonable requests from FDA concerning clinical trial design. Small start-up companies have had to close their doors because of a lack of funds resulting from the unreasonable amount of time spent responding to FDA requests without obtaining final IDE approval to begin their clinical studies. Because of the broken IDE process, more and more U.S. device manufacturers are conducting their trials overseas first. Are you aware of these trends?**
    a. **How long should it take FDA to approve these IDEs?**
    b. **How long is it actually taking?**
    c. **Do you have any suggestions of how FDA can improve the IDE process to prevent companies from failing or moving jobs or clinical trials overseas?**

Yes I am painfully aware of the trends of moving trials overseas – I am currently planning exactly this pathway and strategy for at least two of my existing portfolio

companies. And in fact, it is worse than just conducting first trials overseas – we are conducting ALL of our trials, including our pivotal randomized trials, overseas, with no plans for approaching the FDA for several years.

a. The FDA is required to respond to IDE filings within 30 days, and usually does. And it is expected and appropriate that the FDA does not necessarily approve a trial from the first filing without asking for clarifications or more information – these are often complex devices and disease states. It is reasonable for there to be one or two requests for further information before allowing a trial to go forward, in the vast majority of the cases. Allowing time for company response, a "real world" timeline of 4-6 months would be reasonable, and would allow for the initial evaluation and one or two rounds of questions.
b. In actual practice we have personal experience with our company Xtent, Inc. (now owned by Chinese business interests) of the FDA asking round after round of questions for TWO YEARS before granting conditional approval of the IDE. And in practice, a conditional approval is of little use to the company, because IRBs at hospitals will not approve a trial until the conditions of the conditional approval are met – so it is a way for the FDA to stop their clock for reporting purposes, but in reality there is additional delay in getting the conditions removed. Xtent is not an isolated incident. My colleagues in other medical device incubators and other medical device companies have similar experiences.
c. A few suggestions for reducing these timelines are:
    a. Prohibit the agency from asking new questions in subsequent rounds of questioning that could have reasonably been asked in the first round of questions. If company responses to FDA questions require clarification or raise a new question, it is reasonable that the company should need to respond to that. But too often, questions that significantly delay the start of a trial are ones that should have been asked at the outset, but instead are asked six months or more into the IDE process.
    b. As part of (a), management needs to stabilize review team membership. Many times significant new questions that cause significant delays are because staff experienced in the device and disease state are replaced by new staff, who feel the need to go back and reconsider all of the questions and decision made by previous staff. New members to a review team need to be better managed to make sure that new requests are absolutely essential and not points of scientific interest that have little clinical bearing.
    c. Require individual questions to be attributed to the review team member who posed the concern. As it stands today a company receives a list of questions often with little context to help understand them. Typically all communication has to go through the lead reviewer alone. It would help to know which tem member was posing a question – clinical, technical, management, and then to be able to actually communicate with that person directly to understand the question, rather than having to relay it third hand through the lead reviewer.
    d. Require the agency to give preferential weight to prior human clinical trials performed in top-tier countries over animal studies. In the case

of Xtent, spinal disks and many other companies and technologies, the FDA asks for lengthy and expensive animal studies when long term follow-up in significant numbers of human patients in trials performed in top tier international institutions are available.

e. As more and more companies go overseas for clinical trials and receive CE mark before filing an IDE, IDE approvals of CE marks should be some form of simple review of the data that supported the CE mark and then a quick approval.

5. **How does the EU device regulatory system compare to the U.S.?**
   a. **Are the EU regulations more predictable and certain? Why does that matter to device firms?**
   b. **Is the EU process more lenient?**
   c. **What is the approval standard?**
   d. **Does the EU have more safety problems?**
   e. **Are devices less effective in the EU compared to the U.S.?**

Dr. Makower's report did a good job of characterizing the timeline difference between the US and the EU, and the Boston Consulting Group report demonstrated that safety is not significantly different between the two systems. To specifically answer the questions posed:

a. The EU regulations are significantly more predictable and certain than the US. Even in the most complex devices and trials, the EU regulators appear to be more thoughtful or perhaps more organized in their initial approach to reviewing a clinical trial submission than the FDA. Generally speaking, all questions are asked up front upon the first submission, and then the EU regulators are much more interactive and conversational than the FDA during the process of resolving questions and concerns. If a clinical reviewer asks a question, the company can call that person directly to discus the best way to resolve that reviewer's issues. You can be sure when you submit data to resolve the question that it will be satisfactory to the reviewer as long as it meets the requirements previously agreed upon. This results in a much faster, more transparent and collaborative process than that which exists with today's FDA.

b. The EU process is not more lenient than the US, it is just more efficient and collaborative.

c. The approval standard in the EU is proving that your device or system performs according to the requirements defined for that product. The process for determining design objectives of the device or system (design inputs, in the terminology of the ISO regulations), and for proving that the device or system meets those design requirements are well controlled by a series of ISO standards documents which clearly outline the procedures and safeguards. This is in sharp contrast to the patchwork of often outdated guidance documents that the FDA has put out for specific device categories or procedures, policy statements not contained in guidance documents, and unpublished policies used in different branches within the agency.

d. The EU does not seem to have more safety problems. As mentioned, the only published data that we have on the subject is the Boston Consulting Group report which shows that safety concerns as measured by recalls is essentially the same between the two systems.

e. Devices in the EU are often MORE effective in the EU than they are in the US. There are two reasons for this. As mentioned in the area of artificial spinal disks, the EU system is so efficient compared to the US that while US physicians are still stuck with first generation device (which in some cases are so archaic that physicians will not even use them) while the EU physicians and patients have access to fourth generation technology. Additionally, since the financial burden of the regulatory system is so much lower in the EU than the US, these countries, which largely have socialized medicine, actually have more free market competition than the US. As a specific example, the cost and time associated with trying to get a coronary stent to market is astronomical in the US, and this has created a shared monopoly between the three biggest stent makers in the US. There has been little innovation in this field for many years. In the EU, there are many competitors, forcing more development. Additionally, coronary stents are significantly cheaper in the EU due to this competition. So in this case, the higher regulatory burden in the US is significantly increasing US healthcare costs.

6. **During the hearing, with respect to evidence showing that less than 0.5% of 510(k) devices have been subject to a class I recall, one of the witnesses, Dr. Steve Nissen, twice asked the question that if an airline pilot announced that there was a 99.5% chance of a flight reaching its destination safely, would people take the flight. This question seems to suggest that, short of ensuring that a device is certain to be 100% safe it should not be approved for use in patients. Is this approach or mentality driving FDA decisions concerning the approval of medical devices?**

I believe that this is exactly the mentality that is driving FDA decisions today, as I discussed in eh risk:benefit discussion above. To reiterate, there has been a significant decrease in risk tolerance within the agency. All physicians know that there are no completely safe therapies. All premarket evaluations and clinical trials evaluations must be based on an appropriate risk:benefit analysis. The agency seems to have shifted over the last couple of years to an extremely conservative nature. In some cases, medical reviewers within the agency contradict the risk:benefit opinions of world renowned experts in a given clinical area to err on the conservative side.

In the evaluation of risk:benefit, reviewers take their lead from Agency management, and to some extent management takes its cue from Congress. Many of the issues related to clarity and approval times can only be solved when Congress gives clear direction to management, and holds management accountable for adjusting its expectations back to a more balanced view.

Congress also needs to understand the impact that it has on the Agency and the perception of what appropriate risk tolerance is. Previous leadership of this subcommittee and of Energy and Commerce helped swing the pendulum towards today's extreme conservatism with its handling of the uproar over the whistleblowers' letter of 2008, and with several instances where agency management was called to testify to defend itself after device failures or recalls. I applaud today's leadership for taking a more balanced view, and I urge this and

future leadership to continue to recognize what patients and physicians face every day – there is no benefit without risk.

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The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington D.C. 20515

Dear Chairman Pitts;

Thank you again for the opportunity to testify at the February 17, 2011 House Energy & Commerce Subcommittee on Health hearing, "Impact of Medical Device Regulation on Jobs and Patients." I am pleased to respond to your request for written responses to the questions as outlined in your letter. My responses are given in my individual capacity and as an academic. I hope these responses are useful to you and the members of the Subcommittee.

Question 1: During the hearing we heard testimony from Dr. Nissen regarding a report which also examined Class I recalls: Would you comment on the study published this week in the "Archives of Internal Medicine"?

a. How did those study authors end up with recall results that are much higher than what your study found?

You have requested my analysis of the methodology, accuracy and conclusions of the article entitled "Medical Device Recalls and the FDA Approval Process" by Zuckerman, Brown and Nissen. The article in question describes the results of a study by Zuckerman, et al., into the robustness of the FDA premarket review systems – particularly the 510(k) system.

In summary, the Zuckerman, et al., study starts with a logical data collection process, but fails, however, to actually analyze the data in any meaningful way, ignores key methodological requirements and then seeks to draw pre-ordained conclusions from incomplete raw information.

The Zuckerman, et al., study starts by using the methodology I first reported on at the July 2010 IOM meeting on the 510(k) system. Specifically, the Zuckerman, et al., study collects Class I

recalls reported by FDA during the 2005-2009 time period. They use Class I recalls as the best measure of the safety performance of the premarket review systems.

The initial Zuckerman, et al., data set is very close to what my study found and is also similar to the data assessed by Dr. William Maisel in a separate study. Specifically, Zuckerman, et al., found 113 Class I recalls (after accounting for duplicate records) in the 2005-2009 time period. My study found 118 such recalls. After excluding recalls for counterfeit or quack products, my study analyzed 112 Class I recalls as compared to 113 Class I recalls analyzed by Zuckerman, et al. While I cannot be certain without seeing the actual data set used by Zuckerman, et al., the differences are probably due to one of three reasons: 1) how one deals with recalls conducted pre 2005 but not reported until 2005; 2) minor changes over time in CDRH's recall data base; and 3) how one handles recalls for counterfeit or quack products. These minor differences do not impact the subsequent analysis.

The Zuckerman, et al., initial data set thus actually confirms the data used as the starting point in my study.

The differences in the conclusions of the two studies relate to how the data is then analyzed. It is here that there are major differences, detailed below, in methodology and conclusions.

The Zuckerman, et al., study jumps from the raw number of 510(k) product recalls to conclusions about the robustness of the 510(k) system. It does this by improperly and simplistically comparing raw numbers of recalls between the 510(k) and PMA systems. The authors conclude that the 510(k) system is inadequate because there are approximately 4 times as many 510(k) recalls than PMA recalls. That raw comparison is simply invalid. It ignores the fact that there are approximately 10 times as many 510(k) submissions as PMA submissions each year. For example, under the Zuckerman, et al., approach, one would conclude that employee A has a greater absentee problem than employee B if employee A missed 4 days of work throughout her career while employee B missed one day of work throughout her career. They would ignore the fact that employee A missed those 4 days over a 10 year career while employee B missed one day over a one year career.

The relative number of 510(k) submissions and PMA submission echo this 10/1 disparity.

b. Would you explain the differences in the methodology utilized in your study versus that used in Dr. Nissen's report?

The major concerns and differences with the Zuckerman, et al. article involve how the initial data set of 112 or 113 recalls is analyzed. The authors assert that they are using recall data to assess the performance of the 510(k) system. The concept is that the more robust the safety system the fewer the number of recalls. The theory is correct. However, the methods and assumptions they use unfortunately are flawed to such an extent that the article's conclusions are

not meaningful or reliable. My key concerns with Zuckerman, et al., are detailed under the three bolded subheadings below.

Zuckerman, et al. Fail to Consider the Substantial Difference in the Number of 510(k) and PMA Submissions:

The basic approach or methodology of the Zuckerman, et al., article is to count the number of recalls for 510(k) products, compare that number to the number of recalls for PMA products and, when there are more recalls from the 510(k) group, assert that the 510(k) system is broken. This approach ignores the "denominator" or the number of submissions handled by each system. Data from FDA itself establishes that there are, on average, almost 4,000 510(k) submissions cleared each year while there are only 20-40 new PMAs approved each year. The fact that there are more recalls for 510(k) products than for PMA products is hardly surprising given the 10X difference in number of submissions.

Obviously, one cannot compare the raw number of events without considering the denominator. Even based on the flawed logic (addressed below) of including both premarket and post market events in an assessment of premarket performance, the Zuckerman, et al., analysis is fatally flawed because it ignores the number of products. As mentioned earlier, Zuckerman, et al., found approximately 4 times the number of recalls for 510(k) devices. This is hardly surprising given that there are 10 times the numbers of submissions. Using Zuckerman's own (but flawed) numbers and flawed logic, Zuckerman actually supports the conclusion that the 510(k) system is doing better from the safety perspective than the PMA process - 10 times the number of products with only 4 times the number of negative events.

Of course, comparing raw numbers of events (the "numerator") is meaningless without understand the denominator. Another simple example illustrates this point. Suppose my child comes home and announces that she got a test back and got 5 questions wrong. Am I happy or not? That, of course depends on the number of questions on the test. If she got 5 wrong out of 100 questions, I am most likely pleased (95% is an "A" on almost any test). Conversely, if she got 5 wrong out of 10 questions, I have, shall we say, a different reaction. This simple example demonstrates this key flaw in the Zuckerman analysis. They authors report "4 times" the number of 510(k) recalls – but ignore the fact that there are 10 times the number of submissions.

This fatal methodological or logic flaw alone renders any conclusions from the Zuckerman, et al., study unusable.

Zuckerman, et al., Fails to Consider the Reason for the Recall:

Furthermore, the Zuckerman, et al., analysis fails to consider or even acknowledge a second critical factor – namely the reason for the recall. If one is using recalls to measure the robustness of the premarket review system, one should only consider recalls that are related to premarket

systems. Many recalls are for post market manufacturing or labeling issues. The robustness, or lack thereof, of the premarket review system is irrelevant to these recalls.

For example, assume that a product is approved or cleared in 2005. In 2009, an employee makes a mistake and places the wrong label on the product. In order to prevent the use of the wrong product, the company conducts a recall. The premarket review system, clinical trials, etc. are absolutely irrelevant to these issues. Changing the 510(k) or PMA premarket review systems will not impact the number or severity of such recalls at all.

Many of the actual 510(k)s included by Zuckerman, et al., in their analysis echo this fact pattern of post market reasons for the recall. For example, in 2007, a company conducted a Class I recall (Z-0662-2007) for a product that had been cleared via the 510(k) system three years earlier (K034012). The product was explicitly cleared to be sold in a non-sterile condition. Unfortunately, several years after the product had been cleared, 56 units were mislabeled as being sterile. A Class I recall followed. This labeling mistake had nothing to do with any premarket review process, requirements or clinical trial (or lack thereof). This is a classic post market quality system (or "QSR") issue under 21 CFR 820. Changing the 510(k) premarket clearance system would not have prevented this recall.

By failing to exclude post-market related recalls such as this labeling mistake from the analysis of the premarket 510(k), the Zuckerman, et al., assessment exhibits a major methodological flaw.

This flaw is significant. Based on our analysis of 112 Class I recalls, about 55% of such recalls are related to post market issues and not to pre-market matters. Other studies echo this rate as does FDA's own data. Therefore, more than half of the data used by Zuckerman, et al., should not have been included in any analysis of the premarket 510(k) or PMA systems. This problem is especially concerning given that the Zuckerman analysis depends upon the raw number of Class I recalls.

This methodological error also impacts the ratio of recalls to submissions or clearances. Essentially, the 510(k) system is performing more than twice as well as Zuckerman, et al., would lead the unwary reader to conclude.

Including irrelevant data artificially skews the data and renders any conclusions from the Zuckerman, et al., article unreliable.

Zuckerman, et al., Confuses Device Classification with Recall Class:

In Zuckerman, et al., the authors assert that products subject to a safety (or Class I recall) are "high risk" devices that should go through the approval process for high risk devices (Class III devices). The authors criticize FDA for permitting devices that have been subject to Class I recalls to be cleared for market under any system other than the Class III/PMA process.

This assertion fundamentally confuses approval classification with recall classification. The different nomenclature used for approval classification and recall classification reinforce this difference. High risk devices are labeled "Class III" for approval purposes. High risk recalls are called "Class I" recalls. This nomenclature is reversed for low risk or "Class I" exempt devices and Class III – low risk recalls.By statute (21 U.S.C. §360c), the approval classification (Class III – generally PMA, Class II – generally 510(k) or Class I exempt) is based on the levels of control needed to provide a reasonable assurance of safety and effectiveness. Class I products are those for which "general controls" are sufficient to provide the reasonable assurance of safety and effectiveness.[1] Class II/510(k) products require more than general controls and so are subject to "special controls" and related specific obligations. Special controls can include a bevy of product type specific requirements applicable to both pre market requirements and post market requirements.[2] If special controls and general controls are not sufficient to provide the reasonable assurance, the product goes through the PMA process. By statute, the focus is on the types of controls needed and the use of the product by the intended patient group for the intended uses.[3]

The following tables provide a general comparison of the approval classification system and the recall classification system.

Table 1: Product Classification and Review/Clearance Process by Device Risk Type

	Product classification	**Review or Clearance Process[4]**
High risk devices	Class III	PMA
Medium risk devices	Class II	510(k) / Special Controls
Low risk devices	Class I	Exempt / General Controls

[1] General controls can include any of a variety of quality system requirements including, but not limited to, design controls, product controls, accepted standards, corrective and prevent action systems (often called "CAPA" systems) and supplier controls.

[2] More details regarding special controls and 510(k) processes can be found in the statute (see, for example, 21 U.S.C. §360c(a)(1)(B).

[3] 21 U.S.C. § 360c(a)(2).

[4] Note that this is a general overview. There are exceptions including a few situations in which a high risk Class II devices can be governed by the PMA process and vice versa.

Table 2: Risk-Based Recall Classification

	Recall classification	Product Classification
High risk recall	Class I	Any/All
Medium risk recall	Class II	Any/All
Low risk recall	Class III	Any/All

Recall classification is based on the safety issues related to the violative product, and is separate from the product classification. The recall risk can be high or low regardless of the approval classification. For example, everyone (including Zuckerman and Nissen) should agree that a tongue depressor is a low risk device. No clinical trial is needed to provide data showing that tongue depressors work. General controls covering matters such as sterility and the absence of splinters are more than adequate – if followed. This is a classic Class I exempt device on the approval side. But suppose that the tongue depressor gets contaminated with some deadly bacteria. The risk of this violative product may well be high enough such that this is a Class I safety recall. As can be seen, one should not conclude that approval classification and recall classification are the same things or should be assessed in the same fashion.

Summary:

The following table summarizes the similarities and key differences between the studies:

	Hall Study	Zuckerman/Nissen Study	Comments
Conceptual approach	Use Class I recalls to assess safety performance of 510(k) system	Same	
Starting data set	112 Class I recalls	113 Class I recalls	No meaningful difference
Assessed reasons for recalls	Yes	No	Reason for recall is critical to assessing premarket performance
Compared 510(k) and PMA performance using relative number of submissions	Yes	No	One can't compare two "numerators" without knowing the denominators
Separated approval risks present at premarket stage from standalone post market risks	Yes	No	Approval classification criteria are very different than recall classification criteria

c. Are there inaccuracies in the study regarding the laws governing medical devices?

Unfortunately, the Zuckerman, et al., article includes a significant number of misstatements about the law. For example:

- The article states that PMA devices can be used as a predicate for a 510(k) submission. That is not correct. See, for example, 21 C.F.R. §807.92.
- The article states that the "least burdensome" provisions were added by Congress in 2002. That is not correct. Rather, these provisions were passed by Congress in 1997 as part of FDAMA.
- The article states that the definition of "substantial equivalence" was changed post 2002. That is not correct. This definition existed in the statute long before 2002.
- The article states that clinical trials are not required for 510(k) devices. That is not correct. In fact, FDA has the explicit authority to require clinical trials when appropriate and actually does so in 10-12% of all 510(k) submissions.
- The article states that all Class III devices must go through the PMA. To the contrary, FDA has the explicit authority to review Class III devices under the 510(k) system if the product meets the risk profile appropriate for 510(k) devices.

These multiple errors involve important aspects of the premarket review systems. These multiple errors cast doubt on the overall validity of the study and the peer review process used by the editors prior to publication. Can one trust the conclusions of any article with this many factual errors?

Question 2: During the hearing, with respect to evidence showing that less than 0.5% of 510(k) devices have been subject to a Class I recall, one of the witnesses, Dr. Steven Nissen, twice asked the question that if an airplane pilot announced that there was a 99.5% chance of a flight reaching its destination safely, would people take that flight. This question seems to suggest that, short of ensuring that a device is certain to be 100% safe, it would not be approved for use in patients. Is this approach or mentality driving FDA's decisions concerning the approval of medical devices?

Congress has long recognized two critical realities of medical devices. First, all devices present at least some risk. This is particularly true of devices of medium risk (i.e. 510(k) devices) and high risk (i.e. PMA devices). For example, any implantable device or device that penetrates the skin carries with it some risk of infection. A device that has no risk is a device that has no value. It is frankly silly to contend that medical devices must be 100% safe – that is just impossible and illogical.

Second, Congress has explicitly recognized that there must be a balance between safety, effectiveness and patient access to beneficial medical devices. The more burdensome the premarket process, the fewer devices actually make it to patients and those that do make it to market slower. Congress recognized this balance and so established the statutory standard of a "reasonable assurance" of safety and effectiveness.[5] This "reasonable assurance" standard

[5] 21 U.S.C. §393(b).

instructs FDA to balance safety, effectiveness and access. Someone asserting that the statutory standard is 100% safety either doesn't know the statutory system, or is ignoring it.

It is important to put medical device risks into perspective. Approximately 0.3%-0.5% of 510(k) submissions are subject to a Class I (high risk) recall during a 5 year study period. Compare this to the 2.3% of Medicare/Medicaid patients that experience a safety issue in the hospital. Also, approximately 15% of all seniors receive a potentially unsafe prescription. Some industry critics have asserted that 2-5,000 people die each year from medical devices.[6] Many of these are due to issues outside the scope of any premarket system. This number must be compared to the 98,000 deaths per year attributed to medical error. From a public health perspective, it appears to me that the more important issue is medical error not medical devices.

If one accepts Dr. Nissen's views on safety, no one would ever go to his hospital or any other hospital.

The question is then how FDA is actually implementing the Congressional mandate that medical devices should be made available to patients and physicians after establishing a "reasonable assurance" of safety and effectiveness. Many stakeholders believe that CDRH is over concerned with safety – being almost completely risk averse – while not sufficiently considering patient benefit and patient right to make their own medical decisions. While there is no hard data directly on point, the data that does exist supports this concern. For example, in the last several years there has been:

- a 59% increase in total time to decision on 510(k) submissions;
- a significant (16%) increase in 510(k) submission denials (technically called non substantial equivalence or NSE determinations);
- a 37% increase in requests for additional information; and,
- a 23% increase in number of review cycles.

This data reflects a more risk averse agency.

Multiple reports from industry also assert that FDA has become more concerned with risk and less comfortable with a risk/benefit assessment in which risk plays any significant role. As a result, industry reports that products are available in Europe before the US and that substantial research and development activities are moving out of the United States.[7]

Overall, the available data and reports from stakeholders point to an agency that is currently more risk averse and which has changed the risk/benefit calculus used by CDRH in the past.

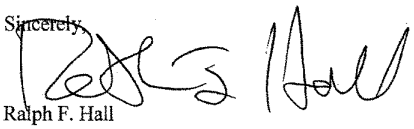
[6] This number is open to substantial debate. For purpose of this comparison, we will use this figure.

[7] It must be noted that FDA disputes these industry views and has challenged the methodology of studies finding longer review periods in the United States than in the European Union.

Finally, it is important to note whose voice is usually conspicuously absent from witness panels on FDA approval processes and performance. We rarely hear from the patient who needs a therapy but one isn't available. The balance of risk and benefit must include not only the risk to those using a particular device but also the lack of benefit and the disease risk faced by patients for whom no therapy or device is on the market. These voices must be part of the debate between risk and benefit.

Thank you again for the opportunity to respond to these questions. I would be pleased to answer any other questions you or the members of the Subcommittee may have.

Sincerely,



Ralph F. Hall
Distinguished Professor and Practitioner
University of Minnesota Law School

cc: The Honorable Frank Pallone, Jr., Ranking Member
Subcommittee on Health

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