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Testimony of Rita F. Redberg, MD, MSc.
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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