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**BEFORE THE
HOUSE COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH**

**MEDICAL DEVICES:
ARE CURRENT REGULATIONS DOING ENOUGH FOR PATIENTS?
JUNE 18, 2009**

INTRODUCTION

Chairman Pallone, Ranking Member Deal, Distinguished Members of the Committee. My name is Dr. William Maisel. I am a practicing cardiologist at Beth Israel Deaconess Medical Center and Assistant Professor of Medicine at Harvard Medical School in Boston. I am also Founder and Director of the Medical Device Safety Institute (www.medicaldevicesafety.org), an industry-independent, non-profit organization dedicated to improving the safety of medical devices. I have served as a consultant to the FDA's Center for Devices and Radiological Health (CDRH) since 2003 and I have previously chaired the FDA's Post Market and Heart Device Advisory Panels. Thank you for the opportunity today to speak about medical device regulation and to discuss areas where improvements can be made to the benefit of millions of Americans who utilize medical devices every day.

Recently, several high-profile device safety issues have raised concerns about the FDA's ability to properly evaluate and monitor the safety and effectiveness of medical devices. FDA has been criticized for taking too long to identify medical device safety concerns and for failing to implement robust scientific standards for device clearance and approval. FDA device physicians and scientists have alleged "serious wrongdoing" at FDA, including the alteration and distortion of scientific and technological findings and conclusions¹. Unfortunately these allegations divert attention from the many superb FDA engineers, physicians, scientists, and public servants who work tirelessly to ensure that only safe and effective medical devices reach the American public.

We are fortunate to have the preeminent medical device regulatory system in the world. The U.S. Food and Drug Administration regulates more than 100,000 different medical devices manufactured by more than 15,000 companies². They annually receive several thousand applications for new and modified devices and they are mandated by Congress to complete their premarket evaluations in a timely fashion³.

When Congress drafted the Medical Device Amendments of 1976, they recognized that medical devices differ from drugs in a number of important ways. Typically, premarket evaluation of drugs includes clinical trials involving thousands of patients. During the premarket evaluation and the postmarket phase, much is learned about the drug, including its pharmacology, its biological effects, and its potential for adverse reactions.

Medical devices are different. Thorough, science-based evaluations of medical device performance can be challenging due to the variability of device types and risks, the

¹ Letter to President Barack H. Obama, April 2, 2009. Accessed 6/26/09 at: <http://finance.senate.gov/press/Gpress/2009/prg040209a.pdf>.

² Maisel WH. Medical device regulation: An Introduction for the practicing physician. *Ann Intern Med* 2004; 140: 296-302.

³ U.S. Department of Health and Human Services. Food and Drug Administration. Center for Devices and Radiological Health. Office of Device Evaluation: Annual Report – Fiscal Year 2006 and Fiscal Year 2007. Accessed May 10, 2009 at: <http://www.fda.gov/cdrh/annual/fy2007/ode/report.pdf>.

difficulty in conducting well-designed clinical trials (for example, the difficulty in conducting blinded or placebo-controlled studies), the heavy reliance on bench testing as a surrogate for clinical performance, and the difficulty in distinguishing device-related adverse events from “expected” procedural or disease-related complications. Perhaps most importantly, unlike drugs, the medical device product life cycle—from conception to obsolescence—is short. While a drug may remain on the market essentially unaltered for decades, rapid technological device advances offer the potential to improve medical device performance, reduce patient suffering, improve health, and sometimes treat previously untreatable conditions. Unnecessarily slowing the device regulatory approval process would be akin to leaving medical device patients with an outdated, antique telephone in an iPhone world.

Nevertheless, it is critical that the safety and performance of medical devices be improved, that the frequency of medical device malfunctions and adverse events be reduced, and that patients and physicians be adequately informed about device clinical effectiveness and risks in a timely fashion. In short, FDA needs to improve its science-based device assessments and decision-making.

PREMARKET EVALUATION

To gain marketing clearance or approval from the FDA for a medical device, a manufacturer must demonstrate reasonable assurance of safety and effectiveness. The specific data required by the FDA to determine safety and effectiveness depend on the type of device, its intended use, and the perceived risk to the patient’s well-being². A device designed to treat a life-threatening condition for which no alternative therapy exists should have a higher acceptable risk than a device designed to treat a benign condition.

Premarket evaluation is designed to confirm the safety, quality, reliability, and predicted clinical performance of the medical device. Data to support safety and effectiveness may include device design verification and validation studies, reliability and engineering analyses, bench and manufacturing tests, statistical risk analyses, animal studies, and human clinical studies. The FDA is required by Congress to use the “least burdensome” approach, meaning that manufacturers are required to provide only data that are necessary to demonstrate safety and effectiveness. In fact, most FDA device marketing reviews do not include human clinical data.

Three medical device regulatory classes (I, II, and III) were defined by the Medical Device Amendments of 1976 depending on the perceived risk of the device². In general, class I and II device types subject to premarket review are required to obtain FDA clearance through the 510(k) process, and class III device types are required to obtain FDA approval through the more stringent PMA process^{2,4}.

⁴ Government Accountability Office. Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process. January 2009. Accessed June 16, 2009 at: <http://www.gao.gov/new.items/d09190.pdf>.

510(k) Process

The 510(k) process requires a device manufacturer to notify FDA before it intends to market a device and to establish that the device is “substantially equivalent” to a legally marketed “predicate” device that does not require a PMA². The FDA’s premarket review of 510(k) submissions is less stringent than that for PMA submissions. For most 510(k) submissions, clinical data are not required and substantial equivalence is determined based on comparative device descriptions and other non-clinical data⁴. The less stringent premarket review also extends to other aspects of FDA’s 510(k) review⁴.

Notably, although Congress intended that higher risk class III devices would be approved through the more stringent PMA process, the Government Accountability Office (GAO) reported in January 2009 that certain types of class III devices continue to be cleared for the U.S. market through the 510(k) process – despite the fact that The Safe Medical Devices Act of 1990 (SMDA) required FDA to reexamine these devices and reclassify them either to class I or II or to have them remain in class III and obtain FDA approval through the PMA process⁴. Nearly two-thirds of the 228 class III 510(k) device submissions that FDA cleared in fiscal years 2003 through 2007 were implantable, life sustaining, or significant risk devices⁴.

One of the class III device types that is still cleared via the 510(k) process is the automated external defibrillator (AED). AEDs are small computers that provide automated heart rhythm analysis, voice commands, and shock delivery to rescue victims of cardiac arrest. The increasingly widespread distribution of AEDs in public places has been an important public health development that has resulted in improved survival of cardiac arrest victims – a leading cause of mortality in the United States accounting for nearly 330,000 deaths annually⁵. Earlier this month, on June 2, 2009, the House passed HR 1380 – the Josh Miller HEARTS Act - sponsored by Representative Betty Sutton (D-OH). The Act is intended to establish a grant program for automated external defibrillators in elementary and secondary schools⁶. Congress certainly recognizes the importance of these devices.

While easy to use, AEDs are technically complex devices. Their life-saving function has prompted their FDA class III designation. However, the 510(k) clearance process for these devices has failed to protect American consumers. According to FDA data from 1996 to 2005, fatal AED-related device malfunctions occurred in 370 patients⁵. In addition, there were 52 FDA recalls and safety alerts affecting nearly 386,000 AEDs and AED accessories. In total, more than 20% - or 1 in 5 - of the nearly 1 million AEDs in circulation have been recalled by the FDA – most often due to electrical or software problems⁵.

⁵ Shah JS, Maisel WH. Recalls and Safety Alerts Affecting Automated External Defibrillators. JAMA 2006;296:655-660.

⁶ Text of H.R. 1380: Josh Miller HEARTS Act. Accessed June 16, 2009 at: <http://www.govtrack.us/congress/billtext.xpd?bill=h111-1380>.

The shortcomings of the 510(k) process, however, run deeper than simple reclassification of class III 510(k) devices. A recent case involving the Edwards Lifesciences Myxo ETlogix annuloplasty ring highlights a concerning reliance by FDA on the medical device industry to police themselves - this despite an inherent conflict of interest sometimes measured in billions of dollars. Annuloplasty rings are implanted via open heart surgery and are used to treat leaky heart valves. The Edwards device was on the U.S. market for two and a half years and implanted into numerous unsuspecting patients despite never being formally cleared by the FDA⁷.

The FDA does permit manufacturers to make a modification to a device without filing a new 510(k) if the manufacturer concludes that the change does not significantly affect the safety or effectiveness of the device or constitute a major change in the intended use of the device^{8,9}. Edwards claimed the device was legally marketed because it incorporated only minor changes to a previously 510(k) cleared device, the Geoform Ring 4200⁷. However, the FDA determined that the company made "the wrong decision" when it marketed its product without FDA clearance⁷. The company recalled the device last fall and formally filed a 510(k) application that resulted in FDA clearance for marketing on April 10, 2009 for the dETlogix annuloplasty ring 5100 (a change in name only from the Myxo ETlogix)⁷. According to the FDA, Edwards will not face any sanctions for having inappropriately marketed the valve⁷.

Remarkably, although manufacturers are required to maintain documentation of their self-conducted regulatory analyses, they are not required to submit documentation to FDA or even to notify the Agency that device modifications have been made⁸. It is apparent that manufacturers have performed numerous other device modifications without the FDA's knowledge and without the Agency's ability to track these changes or their impact on device safety.

Premarket Approval (PMA) Process

The PMA process is the most stringent type of FDA premarket review. Although only 1% of devices listed with the FDA are evaluated via the PMA process, these high-risk devices are implanted into tens of millions of patients and include products such as coronary stents and implantable defibrillators⁴. For fiscal years 2003-2007, FDA reviewed 217 original PMA submissions and 784 supplemental PMA submissions for class III devices (in contrast to the more than 13,000 510(k) submissions during the same time period)⁴.

⁷ Wood S. FDA clears Myxo ETlogix valve ring under new name but disagrees with earlier decision by Edwards that device did not need 510(k). April 14, 2009. Accessed June 16, 2009 at: <http://www.theheart.org/article/960385.do>.

⁸ Grassley calls on FDA to explain letting device maker off hook. Accessed June 16, 2009 at: http://grassley.senate.gov/news/Article.cfm?customel_dataPageID_1502=20502.

⁹ U.S. Food and Drug Administration. Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997. Accessed June 16, 2009 at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm>.

While original PMA submissions typically require clinical data to support device approval, there is no absolute requirement for it to support PMA supplement applications. Indeed, many device modifications for high risk, life sustaining devices occur via the PMA supplement route without supporting clinical data¹⁰. Many medical devices undergo frequent design and manufacturing iterations. Proposed alterations may be brought about by the desire to improve device performance, reliability, ease of manufacturing, or by more practical issues such as contracting with a new supplier of a device component. Even some substantial device alterations may be approved in the absence of clinical data. For example, design changes to a ventricular assist device intended to provide temporary mechanical circulatory support for patients awaiting a cardiac transplant were approved on the basis of only mechanical tests¹⁰. Similarly, FDA approved graft material modifications for a vascular stent system designed to treat peripheral arterial disease in the abdominal aorta on the basis of bench and animal testing without human clinical data¹⁰.

Although there is nothing inherently wrong with bench and animal testing and while many bench tests are designed to satisfy and exceed international standards, bench testing alone cannot account for all patient attributes, physician techniques, or clinical scenarios and may not identify effects that only occur in humans. Bench and animal testing may occasionally identify underperforming devices or device designs that subsequently undergo modifications, although few studies have validated that the results of these tests accurately predict long-term device clinical performance. Premarket clinical device studies can be useful for assessing acute or subacute device performance – although they tend to be underutilized by the FDA. Longer-term premarket clinical device studies are seldom used by FDA to assess long-term premarket device performance as this may substantially slow innovative products from reaching patients in a timely fashion. Notably, premarket clinical testing is typically not useful for identifying rare device failures or unusual device-related adverse events; however, it can identify important safety concerns before unnecessarily exposing large numbers of patients to an underperforming product.

There are a number of reasons why a manufacturer and the FDA would favor evaluation of a device via the 510(k) route rather than the PMA route – most notably the lower cost and lower resource utilization. For fiscal year 2005, for example, the estimated average cost for FDA to review a 510(k) submission was about \$18,200, compared to \$870,000 for a PMA submission⁴. Applicants also pay a substantially lower fee for a 510(k) submission (\$3,693 in fiscal year 2009) compared to an original PMA submission (\$200,725), or PMA supplement (\$30,109-\$150,544)⁴.

It is evident that to best protect the health of American medical device users, the FDA must promote and enforce a higher scientific standard for device clearance and approval – particularly for higher risk devices whose abnormal performance is likely to have adverse effects on patient health. This may best be accomplished by not only clarifying

¹⁰ U.S. Food and Drug Administration. Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process. December 15, 2008.

the status of 510(k) class III devices, but also by closing the loophole that permits many modified devices to be approved via the less stringent PMA supplement route. Additional efforts directed at promoting more robust, scientifically sound, clinically predictive bench testing will minimize product clearance and approval delays and improve overall device safety.

POSTMARKET SURVEILLANCE

During the premarket evaluation, several factors may limit the ability of the FDA to identify and predict which products will perform safely after clearance or approval. There may be questions that cannot be answered in the premarket stage, or an issue may arise after the device is marketed. FDA may require manufacturers to perform post-approval studies as a “condition” of approval to provide on-going evaluation of the device’s safety, effectiveness, and reliability after initial marketing approval. These post-approval studies are most often used to: 1) monitor device performance and safety during the transition from clinical trial to real-world use, 2) assess the long term safety, effectiveness, and reliability of the device, and 3) look for infrequent but important adverse events. These studies may also be initiated to evaluate an emerging public health concern in response to reported adverse events.

In all, the FDA annually receives reports of more than 200,000 device-related injuries and malfunctions, and more than 2000 device-related deaths¹¹ and it is challenging for the Agency to identify patterns of device malfunction among the deluge of adverse event reports. FDA initiatives to better integrate the premarket and postmarket workforces, to develop novel methods of surveillance such as the Medical Product Surveillance Network (MedSun), and to improve tracking of required manufacturer postmarket studies will help.

Although the FDA can theoretically order a product recall in response to observed adverse events or device malfunctions, the vast majority of recalls are voluntarily initiated by the manufacturer. Because of the manufacturers’ inherent financial conflict of interest, the timing and extent of the product recalls are often controversial. FDA often takes weeks or months to officially classify these regulatory actions. During fiscal year 2006, 651 recall actions were initiated involving 1,550 products – again reminding us that FDA product clearance or approval does not ensure device reliability and performance⁵.

Medtronic Sprint Fidelis Implantable Defibrillator Lead Recall

Unfortunately, it is not uncommon for unanswered questions regarding device safety and effectiveness to remain at the time of FDA approval. This creates the potential for a large number of patients to be rapidly exposed to a newly approved product in the absence of long-term follow-up data. For example, close to 268,000 patients had been implanted with the Medtronic Sprint Fidelis implantable defibrillator lead before it was recalled in

¹¹ Center for Devices and Radiologic Health. CDRH FY 2006 highlights. Accessed June 16, 2009 at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm129258.pdf>.

October 2007 after it was determined that the wire was prone to fracture¹². A fracture of the lead, which connects the implantable defibrillator to the heart, may result in serious health consequences, including painful electrical shocks or death.

Mr. Sidney Engler, a patient of mine, was one of the unfortunate 268,000 people to receive this lead when he had an implantable defibrillator placed in February 2006. Mr. Engler is a decorated WWII veteran, having served in Europe from 1943 to 1945. On the evening of August 14, 2008 while preparing to retire for the evening, the simple act of removing his shirt over his head caused his defective defibrillator lead to fracture. Mr. Engler suffered a cardiac arrest in front of his wife. He required CPR and received numerous unnecessary painful shocks from his defibrillator. Fortunately, due to the prompt response of his local EMTs, Sidney survived. Despite a prolonged hospital stay and months of rehabilitation, he has still not fully recovered.

The FDA approved the Medtronic Sprint Fidelis implantable defibrillator lead as a PMA supplement in 2004 on the basis of no human clinical data¹². The original Medtronic defibrillator lead PMA was submitted in 1992; more than 30 supplements had been submitted in the interim and the Fidelis lead bears little resemblance to its original counterpart. In addition to a lack of human clinical performance data, the FDA failed to require a postmarket study to monitor the device's performance. The result was the widespread distribution of a defective product to hundreds of thousands of patients.

Although the FDA does utilize its authority to implement postmarket monitoring strategies, effective postmarket surveillance is undermined by: 1) the lack of uniform criteria for determining which devices require postmarket studies; 2) the repeated inability to get manufacturers to implement these studies in a timely fashion; and 3) the lack of criteria for determining what safety actions FDA should take and when they should take them in response to observed adverse events and product malfunctions.

CONCLUSIONS

Medical devices have enriched and extended the lives of countless people. With the aging of the U.S. population and exponential growth of the medical device industry, device-related malfunctions, adverse events, and patient injuries can be expected to grow. In the wake of high-profile device safety issues and concerns about the FDA's ability to properly evaluate and monitor the safety and effectiveness of medical devices, it is apparent that additional consumer safeguards are needed. Only by demanding more thorough, scientific device evaluations can the FDA hope to reestablish consumer confidence in its ability to protect the public's health.

¹² Maisel WH. Semper Fidelis – Consumer Protection for Patients with Implanted Medical Devices. N Engl J Med 2008; 358: 985-987.