Written Statement of Diana Zuckerman, PhD
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Thank you for the opportunity to testify about the approval process for medical devices.

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

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

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

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

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

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

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

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

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

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

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

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

What are the Policy Implications of High-Risk Recalls?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- **Submissions are not appropriate for use as a denominator** because many devices that were submitted were not cleared, and even those that were cleared were not necessarily ever sold in the U.S. Obviously, a device can't be recalled by the FDA if it is never sold in the U.S. That makes Hall's denominator much too large, and his calculation of the percentage of 510(k) devices that were recalled much too small. His denominator should have been the number of devices that were **cleared** by the FDA and subsequently sold on the U.S. market.

- **Using an average over 10 years to calculate the denominator is incorrect** for several reasons. First, an unknown number of devices that were cleared during the first five years (2000-2004) had already been taken off the market by 2005, when the high-risk recalls started to be evaluated for this study. Secondly, recalls often occur years after a product goes on the market, since in the absence of clinical trials to provide warnings of risks or to gather scientific data after clearance, it can take many years to collect sufficient evidence to warrant a recall. Therefore, calculating the average number of 510(k) submissions from 2000 through 2009 is incorrect, because an unknown number of unsafe devices, especially those cleared most recently, have not been recalled yet.

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

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

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

- However, the Battelle/AdvaMed **denominator included the total number of devices cleared since 1998 (at least 12 years), while calculating recalls only from January 2005 through May 2010 (5.5 years)**. In other words, it did not subtract from the denominator the thousands of devices that were taken off the market for any reason, including but not limited to the estimated 10,000 high-, medium-, and low-risk recalls between 1998 and 2005.[1]

- It also did not subtract from the denominator devices that were cleared between 1998 and 2009 but never sold in the U.S. Those devices should be subtracted from the denominator because they were previously recalled or not on the market during the study period of 2005 through May 2010.

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

Policy Recommendations

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

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

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

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

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

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

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

Conclusions

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

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

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

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