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Hearing on Reauthorization of MDUFA: What It Means for Jobs, Innovation and Patients Subcommittee on Health of the House Energy and Commerce Committee February 15, 2012

On behalf of Public Citizen's more than 250,000 members and supporters nationwide, we thank the Subcommittee on Health of the House Energy and Commerce Committee for the opportunity to share our views on the regulatory oversight of medical devices by the Food and Drug Administration (FDA). For 35 years, Public Citizen's Health Research Group has been involved in research-based consumer advocacy work related to medical device safety.

As the debate on the reauthorization of the Medical Device User Fee Act (MDUFA) has approached, members of Congress have introduced more than a dozen bills, most of which aim to ease the approval and clearance processes for medical devices, often by weakening measures intended to ensure patient safety. The bills reflect the medical device industry's concerted lobbying campaign to expedite medical devices' path to the marketplace during a time in which the debate over MDUFA is shining a spotlight on issues surrounding the FDA. Specifically, the bills aim to accelerate approval and clearance times by such means as:

- further lowering the already weak standards for clearing and approving medical devices;
- substantially weakening the "conflict of interest" prohibition for serving on the FDA advisory committee that oversees device approvals. This would allow more people to review applications for which they have a vested financial interest related to the medical devices under review by the committee;
- expanding the pool of third-party companies that can review device applications to include those with significant financial relationships with the device industry;
- requiring the FDA to rule on third-party reviews of a device within 30 days or grant automatic approval of the device on the 31st day, which would result in the elimination of independent oversight by FDA officials for many devices;
- prohibiting the FDA from disapproving of the methods used in any type of clinical trial conducted by a medical device company. This would include clinical trials conducted on human subjects.

Recent history is replete with examples of devices that were approved or cleared for marketing by the FDA without adequate premarket testing and subsequently caused serious harm to

hundreds or thousands of patients, with some cases resulting in death. Some of these devices have subsequently been recalled, others have not. Furthermore, the history of FDA's postmarket surveillance and enforcement activities for marketed medical devices reveals a consistent pattern of failure to adequately monitor and analyze adverse events related to devices and to remove devices from the market after serious safety signals have become readily apparent. Passage of many of the bills related to medical devices recently introduced in Congress, with few exceptions, would undoubtedly accelerate the rate of patient casualties resulting from unsafe and ineffective medical devices.

We urge subcommittee members to support alternative bills, such as H.R. 3847, the Safety of Untested and New Devices Act (the SOUND Devices Act) of 2012, that would improve patient safety — rather than threaten it. In particular, further legislation is needed requiring the FDA to promulgate new regulations for the premarket approval of medical devices that include mandates for appropriate premarket clinical testing for safety and effectiveness for all moderate- to high-risk medical devices, especially those that are intended to be life-sustaining, life-supporting, or permanently implanted. These are requirements we have advocated for the past 35 years.

I. Major Deficiencies Regarding Current Medical Device Oversight

A. Problems with the premarket approval (PMA) process

Medical devices reviewed by the FDA under the current PMA process generally present the highest level of risk among devices proposed for marketing, many of which are life-sustaining, life-supporting, or permanently implanted. For many such devices, the risks are at least equivalent to, and in many cases significantly greater than, the risks associated with many new drugs. Nevertheless, the current statutory standard for approving or clearing any medical device is "a reasonable assurance of…safety and effectiveness," which is significantly lower than the statutory standard required for approval of a new drug: "substantial evidence" of effectiveness based on "adequate and well-controlled investigations, including clinical investigations" and evidence of safety based on "adequate tests by all methods reasonably applicable to show … [that] such drug is safe for use" (21 U.S.C. § 355[d]). In practice, for most new drugs, at least two well-designed, randomized, controlled, phase 3 clinical trials are required. In contrast, for most medical devices approved under the PMA process, only one controlled study is required by the FDA, and in many cases, the quality of the design of such device studies is subject to a lower standard than that for most clinical trials for drugs (e.g., many are not randomized and use retrospective control groups).

The current low standard for PMA approvals already puts patients at risk by allowing approvals based on poorly designed, uncontrolled trials. In a paper recently published in a peer-reviewed scientific journal, researchers with Public Citizen's Health Research Group described one example of how the FDA's current lower standard for approving medical devices via the PMA process allowed an ineffective, high-risk, implanted medical device to be approved for marketing:[1]

> Consider the vagus nerve stimulator (VNS), a surgically implanted device for treatment-resistant depression. In the only randomized controlled trial (RCT), the device did not

> demonstrate a statistically significant benefit on the primary measure of depression at ten weeks ($p = 0.25$). However, in its PMA application, the company relied on follow-up data at one year in which treated patients were claimed to have improved more than a non-randomized, unblinded, non-concurrent control group ($p<0.001$); both groups were also permitted co-interventions. A psychopharmacology expert in the FDA's drug center advised [the Center for Devices and Radiological Health (CDRH)] that, with similar data for an antidepressant drug, the center would not have permitted the filing of [a new drug application], adding, "it is artificial to us to consider one study for a device (that is negative on face) as sufficient to provide evidence for regulatory efficacy when we require positive studies for a drug." While CDRH initially issued a non-approvable letter, the director of CDRH reversed this decision and approved the device, overruling more than 20 FDA scientists and officials.
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> Subsequently, the Centers for Medicare and Medicaid Services determined that VNS was not "reasonable and necessary," the standard for reimbursement under Medicare. Moreover, it did "not believe there is a treatment benefit directly attributable to VNS." Other third-party payers have also denied coverage for this expensive device.

Recently introduced legislation would seriously undermine standards for PMA approval that are already too weak by explicitly encouraging the FDA to approve PMA applications based on data from studies other than randomized, controlled clinical trials.

From a medical perspective, there is no reasonable substitute for well-designed, randomized, controlled clinical trials in human subjects for assessing the safety, effectiveness, and long-term durability of high-risk medical devices. Pre-clinical bench and animal testing, although important, are insufficient for determining how such devices will perform in human patients. Indeed, the necessity for well-controlled clinical studies has increased over the past few decades as medical devices have become increasingly complex.

Recent experience with metal-on-metal hip implants, such as the DePuy (Johnson & Johnson) ASR XL Acetabular System (ASR), shows the threat to patients when devices are approved without appropriate premarket clinical testing. Metal-on-metal hip implants are devices whose ball-and-socket joints are made solely from metals like cobalt and chromium, in contrast to older hip implants made of other materials, such as metal and plastic. While the FDA could potentially require PMA applications for these high-risk, permanently implanted devices, a current regulatory loophole allows them to be approved through the 510(k) premarket clearance process, which, as discussed below, does not require well-designed, randomized, controlled clinical trials in human subjects. Although these devices appeared to be safe in bench tests, when placed in the human body, the devices can quickly begin to wear, depositing metallic debris in the surrounding tissues that causes severe soft tissue and bone damage.[2] For example, the DePuy ASR hip implant was cleared for marketing in 2005 under the 510(k) process without undergoing any clinical testing. After being permanently implanted in nearly 100,000 patients, the device was recalled in 2010 because of serious problems related to premature failure of the device due to erosion of the metal joint surface and migration of metallic particles into the surrounding tissues and blood-stream.[3, 4] The end result has been characterized by some leading academic physicians as a "public health nightmare."[4] To prevent such public health disasters, all implanted hip

devices should undergo testing in well-designed, randomized, controlled clinical trials to assess their safety, effectiveness, and long-term durability.

Likewise, the history of the FDA's approval and the subsequent marketing of the Wingspan Stent System with Gateway PTA Balloon Catheter (the Wingspan Stent System) provides another dramatic example of the serious harms that can occur in patients when a high-risk medical device that normally would require approval under the PMA process is instead approved under even lower standards, without adequate premarket clinical testing. On August 3, 2005, the FDA approved the humanitarian device exemption (HDE) application for the Wingspan Stent System for the treatment of patients having 50% or greater stenosis (narrowing) of intracranial arteries (blood vessels that supply blood to the brain) due to atherosclerosis and refractory to medical therapy.[5] Under an HDE application, the sponsor was exempt from the effectiveness requirements of a PMA.[6] In this case, the only clinical data provided to FDA prior to approving the Wingspan Stent System was derived from one uncontrolled, single-arm study involving 44 patients who underwent treatment with the device.[7] Such a study was woefully insufficient for establishing a reasonable assurance that this high-risk device was safe, let alone effective.

Although approval of the Wingspan Stent System under an HDE application may have been appropriate, the subsequent history of this device demonstrates the type of dangers that may result if Congress passes legislation allowing high-risk devices to be approved under the PMA process without adequate premarket testing through well-designed, randomized, controlled clinical trials. Results recently published in the *New England Journal of Medicine* from a well-designed, randomized, controlled, multicenter study funded by the National Institute of Neurological Disorders and Stroke demonstrated that the Wingspan Stent System is neither safe nor effective.[8] In this study, patients who had 70-99% narrowing of intracranial arteries and were at high risk of stroke were randomized to receive interventions with aggressive medical therapy plus the Wingspan Stent System or aggressive medical therapy alone. Subjects randomized to the Wingspan Stent System group had a more than two fold-higher incidence of stroke or death in comparison to subjects receiving aggressive medical therapy alone (14.7% versus 5.8%) — a contrast so striking the researchers were forced to stop enrollment in the trial for ethical reasons. Had data from such a study been submitted to the FDA prior to the agency's approval of the Wingspan Stent System, the FDA almost certainly would not have found reasonable assurance that the device was safe and effective and would have denied approval for this unsafe device. Because of the failure to conduct such a well-designed study prior to marketing, it is certain that many patients suffered from strokes and died because they were treated with this inadequately tested device.

Furthermore, the language of some of the recently introduced bills is also flawed because they encourage "the use of surrogate endpoints" as an alternative to "randomized, controlled trials," whereas the use of surrogate endpoints is, in fact, a frequently used method for measuring endpoints in such clinical trials. We note, however, that for most high-risk devices approved under the PMA process, surrogate endpoints would not be reasonable clinical trial markers for assessing safety and efficacy. Direct, clinically relevant endpoints such as mortality and morbidity endpoints (e.g., strokes in subjects undergoing a carotid artery stent procedure) would be more appropriate for most clinical trials of high-risk devices.

Finally, the assessment of the safety and effectiveness of today's complex, high-risk medical devices demands significant time and effort by FDA review staff. Statutory requirements that pressure the agency to carry out reviews more quickly, such as those proposed in in some of the recently introduced legislation, will likely result in short-cuts being taken by FDA staff. Inevitably, patients would be harmed by increased exposure to unsafe and ineffective devices.

B. Problems with the 510(k) premarket clearance process and the determination of substantial equivalence

The 510(k) premarket clearance process is the pathway by which approximately 94% of moderate-risk and many high-risk medical devices — including many that are life-sustaining, life-supporting, or permanently implanted — reach the U.S market.[9] Under the current 510(k) process, the proposed device must be found to be "substantially equivalent" to a predicate device already on the market. Substantial equivalence is evaluated according to the intended use of the device and its technological characteristics *(*21 U.S.C. § 360c[i][1]).

For most medical devices cleared under the 510(k) process, no clinical trials assessing the safety or effectiveness of the devices in humans are conducted prior to clearance for marketing. Furthermore, once a device had been cleared through the 510(k) process, it may serve as a predicate device for subsequent 510(k) submissions, even if the predicate device has subsequently been withdrawn from the market because it was shown to be dangerous or ineffective.

Again, recently introduced legislation would further weaken the 510(k) process by not only retaining the grossly inadequate legal standard — substantial equivalence to a predicate device already on the market — used by the FDA for clearing medical devices under the 510(k) process, but also by constraining the agency's authority to consider important information relevant to the safety and effectiveness of medical devices and by pressuring the agency to take shortcuts to meet the demands for an accelerated review process for increasingly complex medical devices.

The highly respected Institute of Medicine (IOM) in its recently issued report *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years,*[9] criticized the major underpinnings of the 510(k) premarket clearance process more broadly. After extensive, careful study, the IOM concluded that the FDA's 510(k) process for clearing medical devices is fatally flawed and cannot be fixed. In particular, the IOM found the following:

> **The 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices with some exceptions. The 510(k) process cannot be transformed into a premarket evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device.** [emphasis in original]

The IOM fully articulated a compelling and irrefutable rationale for this conclusion. To address its primary conclusion, the IOM recommended the following:

> **The FDA should obtain adequate information to inform the design of a new medical-device regulatory framework for Class II devices so that the current 510(k) process, in which the standard for clearance is substantial equivalence to previously cleared devices, can be replaced with an integrated premarket and postmarket regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle. Once adequate information is available to design an appropriate medical-device regulatory framework, Congress should enact legislation to do so.** [emphasis in original]

Public Citizen strongly agrees with the IOM.

The fundamental failure of the 510(k) process to protect the American public from dangerous and ineffective medical devices has been demonstrated again and again, as numerous devices approved under the 510(k) process have resulted in large-scale harms to patients and many had to be recalled because of their dangers.

For example, over the past decade, multiple synthetic, non-absorbable surgical mesh products designed for transvaginal surgical repair of pelvic organ prolapse (POP) have been cleared by the FDA under the 510(k) process, based on the standard of substantial equivalence to predicate devices. Randomized, controlled studies done after these devices were cleared for marketing under the 510(k) process have shown that while transvaginal POP repair with mesh appears to result in less prolapse being detected on pelvic examination following surgery in comparison to non-mesh repair procedures, the use of mesh does not provide any better outcomes in terms of relief of symptoms and quality of life measures, which ultimately are the clinically significant indicators for measuring treatment success for this condition.[10] Moreover, with respect to safety, a review of the scientific literature demonstrates that use of the non-absorbable, synthetic mesh products for transvaginal surgical repair of POP leads to a high rate of serious complications, many of which require additional surgical intervention and some of which are not amenable to surgical correction and result in permanent life-altering harm to women.[11]

The experience with non-absorbable surgical mesh products for transvaginal POP repair exposes the fundamental failure of the 510(k) premarket notification process to protect the public's health and welfare. Multiple mesh devices specifically designed for transvaginal POP repair were allowed by the FDA to come onto the U.S. market, based only on in vitro and animal-testing data and a determination of substantial equivalence to other surgical mesh products already on the market. Despite a complete lack of clinical data demonstrating that any of these invasive mesh devices was reasonably safe and effective for transvaginal repair of POP, these devices have been heavily promoted by industry and its well-compensated physician consultants. As a result, thousands of women have been seriously harmed, many permanently. Had appropriate premarket clinical trials, like those conducted in the postmarket period, been conducted before the FDA cleared these products for marketing under the 510(k) process, serious harms to these women could have been prevented.

C. Problems with the FDA's postmarket surveillance and enforcement activities

In addition to allowing too many dangerous devices to reach the market, the FDA has also proven inadequate at mitigating the damage from dangerous devices that are in use after evidence of serious adverse events caused by marketed devices becomes apparent.

The current state of postmarket surveillance is ineffective and wasteful. The agency must depend on manufacturers and users such as hospitals to report events of injury or death related to the use of their devices. Manufacturers, in turn, are often unable to locate patients who have been implanted with dangerous devices because they generally do not track which patients have been implanted with their products.

For its part, the FDA has been criticized for making poor use of the data it receives from device manufacturers concerning recalled products. It lacks an internal system to analyze recall trends, which it might otherwise use in future decisions when reviewing a device for PMA approval or 510(k) clearance.

The FDA also has been criticized for failing to take enforcement actions when evidence of unacceptable harm caused by a device becomes apparent or manufacturers violate the law. The IOM, for example, concluded: "When the FDA discovers violations of the law or products that pose unacceptable risks to consumers, it has a wide variety of authorities (or tools) available to try to remedy the situation and to sanction the violators. The committee found that the agency uses those authorities sparingly."[11]

Finally, the prospect of product-safety litigation is theoretically a deterrent to selling unsafe or faulty products. But, in the realm of medical devices, manufacturers enjoy an enormous liability shield. The Medical Device Amendments of 1976 prevent states from establishing "any requirement" that is "different from, or in addition to" requirements in the federal statute that relate "to the safety or effectiveness of the device."[12] In 2008, in *Riegel v. Medtronic*, the Supreme Court cited the 1976 Medical Device Amendments and ruled that federal law preempts all state civil court claims arising from allegedly defective devices, as long as the device in question was approved under the PMA process and the manufacturer followed proper procedure in its application. The result: if the FDA approves a dangerous or defective device through the PMA process, federal law generally prevents consumers harmed by the device from seeking redress in court.

II. Proposals for Improving Medical Device Safety

Ensuring that the medical devices used to treat patients in the U.S. are safe and effective should be the paramount goal of any new medical-device legislation. Patients in the U.S. deserve legislation that improves the review of the safety and efficacy of these devices, instead of weakening it.

The dangers and weaknesses of the existing flawed systems for both premarket review and post-market surveillance of medical devices are readily apparent. On one hand, the current premarket regulation of devices has repeatedly failed to prevent unsafe devices from reaching the market

and injuring and killing patients. On the other hand, devices unequivocally shown to be unsafe after being cleared or approved by the FDA are not being removed from the market in a timely and efficient manner by the agency. Strengthening of applicable Federal statues and the FDA's policies and practices for reviewing and monitoring devices needs to occur in order to increase the agency's ability to protect the public.

A. Premarket Review Processes

Replace the 510(k) process (long-term action). Congress should mandate, in accordance with the IOM's recommendation, that the FDA obtain the necessary information to design a new medical device approval process to replace the 510(k) process. No future medical device premarket review system should rely on "substantial equivalence" to a device already on the market as evidence of safety and effectiveness. Instead, moderate- to high-risk devices, particularly those intended to be life-sustaining, life-supporting, or permanently implanted, should be subject to the same regulatory scrutiny as drugs. Review decisions should rely on "substantial evidence" to support a device's safety and effectiveness.

Modify the 510(k) process (interim, short-term action). Recognizing that replacing the current 510(k) system will take several years to implement, the following revisions to the process should be implemented immediately to improve the safety of medical devices:

- When a device cleared through the 510(k) device is recalled or removed from the market due to safety or effectiveness problems, that device should automatically be removed from the list of devices that can serve as a predicate for a proposed class II device.
- Require manufacturers to provide the FDA with information not just about the immediate predicate device on which a 510(k) clearance request is based, but about the full lineage of predicates.
- To facilitate efficient and effective tracking of the status of marketed devices that a manufacturer might use as a predicate for a proposed device, require the FDA to maintain an up-to-date and easily searchable database of eligible predicates.
- Require the FDA to reevaluate the safety and effectiveness of devices previously cleared under the 510(k) process whenever a device that served as the predicate for those 510(k) clearances is withdrawn from the market due to safety or effectiveness problems. This reevaluation should include any device cleared under the 510(k) process that can be traced back through a chain of 510(k) clearances to the predicate device no longer on the market. This requirement should be imposed retroactively on all devices previously cleared under the 510(k) process.
- Prohibit the clearance of any class III device under the 510(k) process.
- Provide the FDA with authority to require postmarketing surveillance studies, including clinical studies, as a condition of clearance of a device under the 510(k) process

Revise the PMA process. The standard for approving any class III device under the PMA process should be changed to "substantial evidence" of safety and effectiveness. Device submissions reviewed under the PMA process should provide data from at least two well-designed, randomized, controlled, clinical trials conducted by qualified experts that can evaluate the true safety and effectiveness of that device. The current low standard threatens patient safety

when data from poorly designed and uncontrolled clinical trials are considered to be acceptable evidence for establishing the safety and effectiveness of a device during the review process.

Drop the least-burdensome requirement. For all submissions, the requirement that the FDA evaluate devices in a manner that is "least burdensome" upon manufacturers should be eliminated. It is in the best interests of patients for the FDA to make its judgments based on all necessary information.

B. Post-Market Surveillance

Improve device tracking to patients. At present, when a device is recalled because it poses a hazard, no reliable system exists to locate affected patients because, unlike drugs and most other consumer products, medical devices in most cases are not given unique identifier codes that would allow for efficient and effective tracking. Under the current system, most companies only track devices to distributors or user-facilities. Without unique device identifiers, reliable tracking of devices to entities beyond the distributors and to patients is difficult, if not impossible. There are more efficient tracking systems in place for appliances, automobile parts and even pet food today, than there are for medical devices. Under the Food and Drug Administration Amendments Act of 2007, Congress mandated that the FDA establish a unique identification system for medical devices. In the almost five years since the Amendments became law, the FDA has failed to issue regulations implementing this system. Congress should set a deadline in the near future for the FDA to implement such regulations for all devices that pose a moderate- to high-risk to the patients intended to use them.

Improve adverse-event reporting. The FDA should require more thorough standards for reporting adverse events, similar to those used for pharmaceuticals. At present, manufacturers tend to under-report and user-facilities tend to over-report adverse events, but with insufficient specificity. Higher quality mandatory reporting would give the FDA a better database of adverse event information to analyze.

FDA should assert authority in policing unsafe devices. At present, the FDA typically relies on manufacturers to report problems with devices. The FDA often, as in the case of the Wingspan Stent System, has failed to act in the face of convincing evidence that proves certain devices to be unsafe. The agency should utilize more often and more promptly its authority to order recalls of medical devices when the agency deems them to compromise patient safety. All too often, the agency relies on device manufacturers to take action voluntarily, resulting in substantial delays in removing dangerous and ineffective devices from the market.

A recall should be a recall. When a manufacturer does initiate a voluntary recall, the recall must mean the removal of the suspected defective device from market. Communications to customers or user-facilities, like sending warning letters to hospitals, should not be classified as a recall.

Systematically analyze and track recalls. The FDA should be required to systematically collect and assess data regarding all medical device recalls, whether mandated by the agency or voluntarily implemented by manufacturers. As part of this analysis, the agency should determine whether recalls were implemented in an effective and timely manner in order to ensure patient

safety. The FDA also should document the basis for any termination of a recall ordered by the agency. All such information regarding the analysis and tracking of recalls should be maintained in a publicly accessible database on the agency's website.

Restore patients' legal rights. Finally, Congress should pass legislation to restore injured patients' ability to bring claims for injuries caused by defective medical devices. A 2008 Supreme Court decision, *Riegel v. Medtronic*, had held that pre-market approval of a medical device by the FDA preempted most state tort law claims against the device manufacturer. The decision removed a vital and long-standing component of the consumer safety net for medical devices. As a result, patients harmed by unsafe devices are often deprived of their only avenue for seeking compensation for their injuries.

The mechanisms of public safety are failing to protect the public from dangerous devices and instead are protecting device manufacturers' pocketbooks from both proper FDA regulation and from being held accountable in court.

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