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November 1, 2011

Senator Amy Klobuchar
302 Hart Senate Office Building
Washington, DC 20510

Senator Richard Burr
217 Russell Senate Office Building
Washington, DC 20510

Senator Michael F. Bennet
458 Russell Senate Office Building
Washington, DC 20510

Dear Senators Klobuchar, Burr, and Bennet:

Public Citizen, representing more than 225,000 members and supporters nationwide, strongly opposes Senate Bill S. 1700, the Medical Device Regulatory Improvement Act (hereinafter referred to as "the bill"), because, contrary to the bill's title, the proposed amendments to the Federal Food, Drug, and Cosmetic Act would weaken the already inadequate regulatory requirements for medical devices approved under the premarket approval (PMA) process or cleared under the 510(k) premarket clearance process.

Recent history is replete with examples of marketed devices that were approved or cleared for marketing by the Food and Drug Administration (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. Passage of the bill would undoubtedly accelerate the rate of patient casualties resulting from unsafe and ineffective medical devices.

We urge you to withdraw your sponsorship of the bill and develop new legislation that would improve patient safety — rather than threaten it — by 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, particularly those that are intended to be life-sustaining, life-supporting, or permanently implanted. These are requirements we have advocated for the past 35 years.

Our comments regarding specific key provisions of the bill are as follows:

A. Proposed amendments to 21 U.S.C § 360c(a)(3)(D) regarding the PMA process

The bill would insert the following new clause (iii) in 21 U.S.C. § 360c(a)(3)(D):

> *(iii) In carrying out clause (ii), the Secretary—*
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> *(I) shall not request information unrelated or irrelevant to a demonstration of reasonable assurance of device safety and effectiveness;*
> *(II) shall consider alternative approaches to evaluating device safety and effectiveness in order to reduce the time, effort, and cost of reaching proper resolution of the issue;*
> *(III) shall use all reasonable mechanisms to lessen review times and render regulatory decisions;*
> *(IV) shall determine whether pre-clinical data, such as well-designed bench and animal testing, can meet the statutory threshold for approval; and*
> *(V) if clinical data are needed, shall utilize, whenever practicable, alternatives to randomized, controlled clinical trials, such as the use of surrogate endpoints.*

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 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).

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 how the FDA's current lower standard for approving medical devices via the PMA process allowed one 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.

Thus, the proposed bill would seriously undermine standards for PMA approval that are already too weak Regarding subclauses (II), (IV), and (V) above, 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 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. While 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 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 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 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.

Not surprisingly, 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 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 System or aggressive medical therapy alone. Subjects randomized to the Wingspan System group had a significantly greater risk of stroke or death in comparison to subjects receiving aggressive medical therapy alone. Patients in the stenting group had a risk of stroke or death that was double that of the group receiving 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 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, with regard to subclause (V), the language of the bill is flawed because "the use of surrogate endpoints" is not an alternative to "randomized, controlled trials." Rather, it is 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 that proposed in sub-clause (III), 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. Proposed amendments to 21 U.S.C § 360c(i)(1)(D) regarding the 510(k) premarket clearance process and the determination of substantial equivalence

The bill would insert the following new clause (ii) in 21 U.S.C. § 360c(i)(1)(D):

> *(ii) In carrying out clause (i), the Secretary—*
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> *(I) shall focus on whether the device has the same intended use as the predicate device and is as safe and effective as a legally marketed device;*
> *(II) shall not request or accept information unrelated or irrelevant to the substantial equivalence evaluation;*
> *(III) shall review the labeling of the device to assess the intended use of the device, and shall not evaluate issues that do not present a major impact on the intended use as set forth in the labeling;*
> *(IV) shall consider alternative approaches to evaluating substantial equivalence in order to reduce the time, effort, and cost of reaching proper resolution of the issue; and*
> *(V) shall use all reasonable mechanisms to lessen review times and render regulatory decisions.*

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.

Unfortunately, the bill's proposed new clause in 21 U.S.C. § 360c(i)(1)(D) would not only retain 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, it would further weaken the 510(k) process 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.

In particular, subclause (I) would direct the FDA to focus solely on whether a proposed device has the same intended use as a predicate device in making a determination of substantial equivalence (as opposed to looking at *both* its intended use and its technological characteristics, as currently required by statute). This change would exacerbate one of the most serious flaws with the 510(k) process, which the FDA has labeled "predicate creep."[10] Predicate creep occurs because the 510(k) process allows sponsors to identify a predicate device that was itself substantially equivalent to another device that was substantially equivalent to another and so on. Over multiple cycles, a new device may come on the market as "substantially similar" but that is in fact quite dissimilar to the original predicate device. As a result of predicate creep, not only can there be a lack of evidence regarding the safety and effectiveness for each predicate device in the chain of 510(k) clearances, the most recently cleared device can diverge significantly from the original predicate device in terms of technological characteristics and intended uses. Requiring FDA to focus on the intended use of a device, without adequate consideration of technological characteristics and many other factors relevant to patient safety, would further promote predicate creep.

Moreover, 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.[11] 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. Recommendations

Public Citizen urges you to drop your support for S.1700, which would weaken the already inadequate regulatory requirements for medical devices and cause widespread

serious harms to patients and public health. Instead, the Senate should develop alternative legislation that would better protect patients in the U.S. from dangerous and ineffective medical devices. We recommend that such legislation include the following:

- Amend 21 U.S.C. § 360c to require moderate- to high-risk devices, particularly those that are intended to be life-sustaining, life-supporting, or permanently implanted, to meet the same standards as those required for drugs, and include language such as the following:
    - The application for the device must include substantial evidence that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; substantial equivalence means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the device involved; and
    - The application for the device must include adequate tests by all methods reasonably applicable to show that such device is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

- In accordance with the IOM's primary recommendation, mandate that FDA 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 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.

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.

Thank you for your attention to this important matter.

Sincerely,

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cc: U.S. Senate Committee on Health, Education, Labor & Pensions
Senate Majority Leader Harry Reid
Senate Minority Leader Mitch McConnell

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