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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2011-N-0556 — Comments regarding the Institute of Medicine's Report, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*

To Whom It May Concern:

Public Citizen's Health Research Group completely agrees with the main conclusion of the Institute of Medicine's (IOM) Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process (the committee)[1] that the Food and Drug Administration (FDA) 510(k) process for clearing medical devices is broken and cannot be fixed. In particular, the committee found that the legal standard used by the FDA for clearance of medical devices under the 510(k) process — "substantial equivalence" to a predicate device already on the market — fails to ensure that devices are safe and effective. We reached the same conclusion in 1990 when we submitted comments on the draft Safe Medical Devices Act (SMDA) of 1990.[2,3]

We strongly endorse the committee's primary recommendation that the current FDA 510(k) clearance process "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."

We were dismayed and disappointed to see Dr. Jeffrey Shuren, the Director of the FDA's Center for Devices and Radiological Health (CDRH) — acting in lockstep with the device industry — immediately reject the committee's central finding and primary recommendation by stating in a news release issued by the FDA[4] on the day the committee released its report that the "FDA believes that the 510(k) process should not be eliminated."

The FDA's long-standing procedures for clearing medical devices under the 510(k) process are flawed and fail to adequately protect public health because they repeatedly allow dangerous and ineffective medical devices to reach the market.[5] Thousands of patients have been killed and many more seriously injured by dangerous medical

devices over the past 35 years. It is imperative that the FDA resist the overwhelming commercial interests of device manufacturers and promptly implement the IOM's recommendation in order to ensure that the health of millions of future patients treated with medical devices is not jeopardized.

Below we provide more detailed comments: first about the committee's overarching conclusions and recommendations presented in chapter 7 of its report, and then about the selected content and findings presented in chapters 1 to 6.

A. Chapter 7 — CONCLUSIONS AND RECOMMENDATIONS

(1) ***Conclusion 7-1 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.***

As noted above, we completely agree with the committee's conclusion. As the committee correctly points out, the 510(k) clearance process was not designed to evaluate the safety and effectiveness of new medical devices but only to assess their similarity (i.e., substantial equivalence) to predicate devices. A new device cleared under the 510(k) process is at best only as safe and effective as its predicate.

Because of the increasing complexity of medical devices, the problems that result from the deficiencies in the 510(k) process are becoming more pronounced.

In its discussion of conclusion 7-1, the committee stated that "*it is not suggesting that all, many, or even any medical devices cleared through the 510(k) clearance process and currently on the market are unsafe or ineffective*" [emphasis in original]. However, it is important to note that the committee was not charged with evaluating the safety and effectiveness of any specific medical device currently on the market, nor did it undertake any such evaluation. We note that there are medical devices cleared under the 510(k) process and currently on the market that are unsafe and ineffective, such as the multiple non-absorbable synthetic mesh products used for transvaginal repair of pelvic organ prolapse.[6]

(2) ***Conclusion 7-2 Information that would allow an understanding of the extent to which the 510(k) clearance process facilitates or inhibits innovation does not exist.***

We agree with the committee's conclusion. Furthermore, we agree with the committee's assessment that the FDA should not be charged with *promoting* innovation, but instead should seek to *facilitate* it, provided that such facilitation is

secondary to the primary objective of ensuring that medical devices are safe and effective before entering the market.

(3) ***Recommendation 7-1 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.***

Again, we strongly endorse the committee's recommendation. Any efforts to retain a modified version of the 510(k) process will fail to adequately protect the public from unsafe and ineffective medical devices. We agree with the committee's assessment that currently available information reviewed by the committee is insufficient for designing an appropriate new framework. The FDA should move quickly to gather the necessary information to design a new framework.

Furthermore, any new process for premarket regulation should include a requirement for premarket clinical testing for safety and effectiveness for all life-sustaining, life-supporting, or implantable medical devices, a requirement we have advocated for more than 35 years.

(4) ***Recommendation 7-2 The FDA should develop and implement a comprehensive strategy to collect, analyze, and act on medical-device postmarket performance information.***

We agree with the committee's recommendation. As discussed below in greater detail in section F, the committee found that the FDA's postmarketing surveillance system has failed to provide sufficient information about potential harm or lack of effectiveness of marketed devices, including those that went through a premarket approval (PMA) process. The FDA should proceed with the implementation of more robust postmarketing surveillance systems, while simultaneously taking steps to implement recommendation 7-1.

(5) ***Recommendation 7-3 The FDA should review its postmarket regulatory authorities for medical devices to identify existing limitations on their use and to determine how the limitations can be addressed.***

We agree with the committee's recommendation. As discussed below in greater detail in section D(2), the FDA has used its postmarketing judicial and administrative enforcement authorities sparingly. The implicit intent of this recommendation is that the FDA should significantly increase its use of these

authorities in order to more promptly take action to remove unsafe and ineffective devices from the market or to prevent such devices from reaching the market.

(6) ***Recommendation 7-4 The FDA should investigate the viability of a modified de novo process as a mechanism for evaluating the safety and effectiveness of Class II devices.***

Given the lack of clarity regarding the process the FDA currently follows in its implementation of the de novo process, we are unable to judge the merits of this recommendation.

(7) ***Recommendation 7-5 The FDA should develop and implement a program of continuous quality-improvement to track regulatory decisions on medical devices, identify potential process improvements in the medical device regulatory framework, and address emerging issues that affect decision-making.***

We agree with the committee's recommendation. As discussed in greater detail in D(4) below, CDRH has failed to implement a comprehensive quality assurance program to regularly assess the quality, consistency, and effectiveness of the 510(k) process. Such a failure represents one of — if not the — greatest failure of CDRH leadership over the past three decades.

(8) ***Recommendation 7-6 The FDA should commission an assessment to determine the effect of its regulatory process for Class II devices on facilitating or inhibiting innovation in the medical-device industry.***

We would rank this recommendation as being the lowest priority.

(9) ***Recommendation 7-7 The FDA should develop procedures that ensure the safety and effectiveness of software used in devices, software used as devices, and software used as a tool in producing devices.***

We agree with this recommendation. As discussed in greater detail in section G below, device manufacturers are increasingly using software in their medical devices, and this is one of several factors that have led to the increasing complexity of medical devices being cleared under the 510(k) process. The committee also reports that software problems are responsible for an increasing number of recalls.

Because many life-sustaining, life-supporting, and implanted devices rely upon software for proper functioning, and software errors can cause serious adverse events, including death, this recommendation should be given high priority.

(10) ***Recommendation 7-8 The FDA should promptly call for PMA applications for or reclassify Class III devices that remain eligible for 510(k) clearance.***

We agree with this recommendation. We and others have been calling for such action for several years.[5,7]

B. Chapter 1 — INTRODUCTION

(1) Page 13, second paragraph — The report offers the following as one justification, among others, for requiring randomized clinical trials prior to approval of drugs, but not medical devices:

> *Drugs may be used by thousands or millions of consumers; but many devices are used by only a small number of patients, so large premarket randomized, controlled studies to detect rare events or small differences between products may not be feasible.*

This is not a reasonable justification for allowing manufacturers to market medical devices without first providing safety and efficacy data from well-designed clinical trials, particularly for new devices that are intended to be life-sustaining, life-supporting, or implanted. On the one hand, many such devices approved under the 510(k) process have been or will be used in many thousands of patients, and it certainly would have been feasible to conduct well-designed studies to evaluate their safety and effectiveness before being marketed. For example, non-absorbable surgical mesh products have been surgically implanted in hundreds of thousands of women for repair of pelvic organ prolapse, and it would have been feasible to conduct well-designed clinical trials before these devices were marketed and used widely. Randomized, controlled studies done after these devices were cleared for marketing under the 510(k) process have shown that these devices are both unsafe and ineffective.[6] Had these clinical trials been conducted before the FDA cleared these products for marketing under the 510(k) process, serious harms, including death, to tens of thousands of women could have been prevented.

On the other hand, some drugs for rare diseases that are used only in small numbers of patients have been tested successfully in well-designed clinical studies involving a limited number of subjects prior to being approved by the FDA. For example, the biologic canakinumab [Ilaris] was approved by the FDA for the very rare group of disorders called Cryopyrin-Associated Periodic Syndromes after well-designed studies involving a small number of subjects were completed.[8]

(2) Page 14, first paragraph — The committee stated the following regarding the definition of innovation:

> *In the context of the present report, the committee defined innovation as something that improves the quality of, efficiency of, or access to healthcare. Class II devices do not need to be shown to be innovative to be cleared for marketing. Premarket regulation of moderate-risk devices*

can facilitate innovation that improves public health by making safe and effective devices available to consumers in a timely manner.

We agree with the committee's definition of innovation and its conclusion that a device cleared under the 510(k) process need not be innovative. We also agree that any process for premarket regulation of moderate- and high-risk devices, particularly any devices that are intended to be life-sustaining, life-supporting, or implanted, should be shown to be safe and effective before being made available to consumers.

(3) Page 16, Box 1-1 and first paragraph — The committee identified the following as attributes of an ideal medical-device regulatory system:

- *The process should be based on sound science.*
- *The process should be clear, predictable, straightforward, and fair.*
- *The process should be self-sustaining and self-improving.*
- *The process should facilitate innovation that improves public health by making medical devices available in a timely manner and ensuring their safety and effectiveness throughout their lifecycle.*
- *The process should use relevant and appropriate regulatory authorities and standards throughout the life cycle of devices to ensure safety and effectiveness.*
- *The process should be risk-based.*

We generally agree that these are reasonable attributes of an ideal medical-device regulatory system. However, the fourth bullet appears to inappropriately give equal weight to facilitating innovation and ensuring the safety and effectiveness of medical devices. Ensuring the safety and effectiveness of medical devices must be the primary attribute of any new medical-device regulatory system and facilitating innovation should be relegated to a secondary goal.

(4) Page 16, second paragraph — The committee made the following observation:

The committee recognizes that no premarket regulatory system for medical devices can guarantee that all devices are completely safe and effective. That would set an impossible threshold. Any regulatory system must balance medical devices' risks and their potential public health benefits. Given that a perfect premarket regulatory system is unrealistic, it is essential to have effective postmarket oversight of medical devices.

We agree with the committee's observation and its conclusion that effective postmarket oversight of medical devices is essential. The same is true for drugs. As the committee notes in detail in later chapters of its report, current FDA postmarket oversight of medical devices is completely inadequate.

C. Chapter 2 — KEY MEDICAL-DEVICE LEGISLATIVE AND REGULATORY ACTIONS

(1) Page 25, third paragraph — The committee made the following finding:

> ***Finding 2-1 The safety and effectiveness of preamendment Class II medical devices has not been systematically reviewed. Continued use in clinical practice, however, provides at least a level of confidence in the safety and effectiveness of preamendment Class II medical devices still on the market.***

We disagree with the committee's assessment that "continued use in clinical practice" provides some level of confidence in the safety and effectiveness of preamendment Class II medical devices. History is replete with examples of medical products that have been used for long periods of time and ultimately were shown to be unsafe and/or ineffective.

(2) Page 25, last paragraph — The committee made the following finding:

> ***Finding 2-2 The 510(k) clearance process was not designed in 1976 to evaluate the safety and effectiveness of new medical devices but only to assess their similarity to preamendment devices.***

We agree with this finding.

(3) Page 26, first paragraph — Regarding the FDA's implementation of the Medical Devices Amendments (MDA) of 1976, the committee correctly highlighted two factors, among many, that have contributed to the failures of the 510(k) process and allowed dangerous and ineffective medical devices to reach consumers:

> *Congress did not define substantial equivalence in the 1976 amendments, and the legislative history contains a one-paragraph discussion that is, at best, ambiguous (FDA, 2010). Because of resource limitations, the FDA tended to find that postamendment devices were substantially equivalent to preamendment devices. To rule otherwise would increase the need for personnel to review PMA applications or to reclassify postamendment devices down from Class III, and both would have been labor-intensive activities. Furthermore, as time passed after 1976, the FDA adopted a practice of permitting a chain of devices to link a new postamendment device to earlier postamendment devices that ultimately could be traced back to a preamendment device; that is, Device A might be found substantially equivalent to Device B, which had been found equivalent to Device C, which had been found equivalent to Device D, and so on back to a preamendment device (FDA, 2010). The effect of those actions was that the 510(k) process evolved into a system that tended to find substantial equivalence far more often than nonequivalence. Between*

fiscal years 1976 and 2009, only 1–4% of 510(k) notifications submitted annually were found by the FDA to be not substantially equivalent.

The committee first pointed out that chronic staff and resource limitations at CDRH created circumstances under which agency staff have been pressured to routinely determine that new devices submitted for clearance under the 510(k) process are substantially equivalent to a marketed Class I or II device in order to avoid the additional burdens that would be placed upon the agency if more devices instead were deemed to be not substantially equivalent to already marketed devices and instead required submission of PMA applications.

The committee then noted what we have long considered to be one of the most serious flaws with the 510(k) process, which FDA has labeled "predicate creep."[9] 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. This iterative process permits a scenario in which, over multiple cycles, a new device can be quite dissimilar to the original predicate device — so-called predicate creep.

For example, the Pathwork Tissue of Origin Test, cleared in 2008, is a microarray kit that compares the RNA expression pattern from a tumor with an unknown primary to the expression patterns of 15 common tumors.[10] This device's predicate device was the BioPlex 2200 Medical Decision Support Software, a software algorithm cleared in 2005 that assists in diagnosing autoimmune disorders by matching enzyme-linked immunoassay results to a database of sera from patients with autoimmune disorders.[11] This device, in turn, had been declared substantially equivalent to the Remedi HS Drug Profiling System, an algorithm-based diagnostic kit cleared in 1995 that tests for illicit drugs. Thus, a screening test for illicit drugs ultimately allowed for the clearance of a malignancy diagnostic test, simply because both use computer programs to compare samples to an existing database.

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 the chain in terms of technological characteristics and intended uses.

(4) The committee made the following finding:

Finding 2-5 With limited exceptions, a determination by the FDA that one device is "substantially equivalent" to another device does not reflect an FDA evaluation of the safety or effectiveness of either device.

We agree with this finding.

D. Chapter 3 — COMPONENTS OF U.S. MEDICAL-DEVICE REGULATION

(1) Page 41, last paragraph — Regarding the special controls for Class II devices, the committee concluded the following:

> *For a number of reasons, however, special controls have not transformed and cannot transform the 510(k) process into one based on safety and effectiveness rather than one based on substantial equivalence to a predicate device.*

The committee proceeded to describe several reasons for its conclusion. We agree with the committee's conclusion and the underlying rationale for it.

(2) Pages 43-53 — The committee identified the administrative enforcement and other powers available to the FDA when the agency discovers violations of the device laws or products that pose unacceptable risks to consumers, empowering the agency to remedy the situation and to sanction the violators. The committee reported the following information regarding the frequency with which FDA has used each of these authorized powers:

Judicial Enforcement Powers:

- *Seizure and forfeiture of violative product … The FDA has advised the committee that in the period FY 2001–2008, it has successfully brought 13 seizure actions (Desjardins, 2011).*
- *Injunction. The FDA can seek a federal court order restraining persons from violations of the [Federal Food, Drug, and Cosmetic Act (FFDCA)]…The FDA has informed the committee that in the period FY 2001–2008, it obtained 12 injunctions related to medical devices (Desjardins, 2011).*
- *Criminal prosecution … Criminal Investigations successfully obtained 212 criminal convictions for violations of the law in the period FY 2001–2010, which resulted in fines and restitution in excess of $577 million (Desjardins, 2011).*

Administrative Enforcement Powers:

- ***Banning a Device.** The FDA may ban a device from sale if it finds that the device "presents substantial deception or an unreasonable and substantial risk of illness or injury"… According to the FDA, this authority has been used only once since it was established in 1976 (Desjardins, 2011).* [Emphasis added]
- ***Recalling a Device** … The agency advised that it has not formally tracked recall orders but believes that the authority has been used at least three times in the last 20 years (Desjardins, 2011).*

- ***Ordering Risk Notification about a Device*** *... The FDA has not tracked the use of this authority (conferred in 1976) but advises that it has not been used many times. It was used once in 2010 (Desjardins, 2011).*
- ***Imposing Civil Money Penalties*** *... According to the FDA, civil money penalties have been imposed seven times in the period FY 2001–2008 (Desjardins, 2011).*
- ***Detaining a Device in Anticipation of Seizure*** *... The FDA does not track the numbers of detention orders that precede seizure. The agency informed the committee, however, that use of this authority is difficult because of the statutory timeframe of 30 days, which is generally not sufficient to process a seizure action (Desjardins, 2011).*
- ***Detaining and Denying Entry of Devices Offered for Import into the United States*** *... In the period 2002–2010, over 17,500 devices and almost 1200 diagnostics were refused entry into the United States by the FDA (Desjardins, 2011).*

The committee made the following findings regarding the FDA's use of these authorized powers:

> ***Finding 3-1 The Food and Drug Administration has a wide array of tools to address safety risks that are discovered to be posed by marketed devices.***
>
> ***Finding 3-2 The Food and Drug Administration has not used the tools at its disposal extensively. The Center for Devices and Radiological Health has suggested that there are important limitations in their use. The committee identified some procedural burdens on the exercise of these tools, but these burdens do not in themselves explain the historical and continuing sparse use of the tools.***

Given the number and scope of medical devices approved under the 510(k) process over the past 35 years, CDRH's failure to aggressively use all judicial and administrative enforcement powers available to the agency in response to safety concerns about marketed devices has resulted in unacceptable delays in removing unsafe medical devices from the market and preventing serious harms to patients. It is important to note that the committee rejected CDRH's excuse for not using these powers more frequently (i.e., "procedural burdens"). The failure of the agency to invoke these judicial and administrative powers more frequently in order to protect public health demonstrates a failure of leadership at CDRH that spans many years.

(3) Page 56, fifth paragraph — The committee noted the following regarding the evolution of the 510(k) process:

> *The most important development after 1976 was the evolution of the 510(k) clearance process from a transitional tool for preclearance of*

postamendment devices to a permanent and dominant means of premarket review for most postamendment devices.

The committee pointed out that the 510(k) process, when initially implemented under the 1976 MDA, was never intended to be a permanent process for allowing many Class II medical devices to reach the market.

(4) Pages 63-65, "**Quality Assurance**" section — The committee made the following observations and finding regarding CDRH's quality assurance procedures for the 510(k) process:

> *The **Department of Health and Human Services [(HHS)] inspector general (IG) in 1990 determined that CDRH lacked a comprehensive quality-control program to evaluate and critique the adequacy of the 510(k) review process independently**. Three years later, the inspector general issued a follow up report that concluded that CDRH had focused its quality efforts primarily on the administrative aspects of the 510(k) process, not on the scientific validity of the review decisions ...* [Emphasis added]
>
> ***CDRH has long required device manufacturers to operate a quality system**. In an oversimplified description, the regulations prescribe a continuous-improvement process in which specifications and operating procedures are established, persons who have appropriate backgrounds are trained in the procedures, execution of the procedures is properly documented, and the resulting output is monitored for conformity to the specifications. When a deviation occurs, the manufacturer is to undertake a root-cause analysis and then implement a corrective action and preventive-action plan to address the root problem and prevent its recurrence (for example, by revising operating procedures, retraining employees, or revising specifications). The continuous-improvement process is overseen by a quality manager or group and executive management of the company. Those basic principles are as applicable to the making of 510(k) clearance decisions — and any other regulatory decisions (such as PMA application approvals and the use of postmarketing tools to address emerging safety concerns) — as to the production of medical devices.* [Emphasis added]
>
> *The absence of a quality system for the 510(k) process since its inception has important consequences for the future of the process. Prior 510(k) clearance decisions are by law binding on the FDA unless a predicate product is removed from the market by the FDA or declared adulterated or misbranded by a federal court. The agency is concerned that it may not have clear legal authority to rescind prior decisions on the grounds that the substantial-equivalence decision was scientifically wrong (Shuren, 2011).*

> *... About 120,000 510(k) submissions have been cleared over the last 35 years (Tillman, 2010). As described in Chapter 2, those actions have by and large built on a chain of devices that link a new postamendment device to earlier postamendment devices that ultimately could be traced back to a preamendment device from 1976.* ***CDRH has never had an effective quality assurance system in the 510(k) process.*** *In addition, at least in the early years of implementation, the FDA may have biased the review process in favor of finding substantial equivalence to avoid the administrative consequences of placing too many devices in Class III (OTA, 1984).* ***Today, CDRH cannot reconstruct the "piggy-backing" of devices without a manual review of perhaps thousands of files*** *...* [Emphasis added]
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> ***Finding 3-5 The committee agrees with the CDRH 510(k) Working Group that the Center for Devices and Radiological Health does not have "an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program."***

The failure of CDRH to implement a comprehensive quality assurance program to regularly assess the quality, consistency, and effectiveness of the 510(k) process represents one of — if not the — greatest failure of CDRH leadership over the past three decades. The complex and widely used 510(k) process has been the primary pathway for allowing most moderate- and high-risk devices to reach the market. As such, it has tremendous impact on public health. Implementation of a comprehensive quality assurance program to continuously monitor and assess such a process would be a fundamental component of any good business model. Nevertheless, as the committee pointed out, whereas CDRH has required manufacturers of medical devices to establish quality assurance systems, it has not held itself to the same standard. Such a double standard is unacceptable and reckless.

E. Chapter 4 — THE 510(K) CLEARANCE PROCESS

(1) Page 72, last paragraph, continuing on page 73, first paragraph — In its discussion of substantial equivalence, the committee highlights another important flaw in the 510(k) process:

> *In contrast, the change [regarding the term "substantial equivalence" under the SMDA of 1990] did not require reliance on the best predicate device, so a product that was truly inferior to the current state of the art could still enter the market if the manufacturer could identify any predicate that had not been removed from the market and to which it was substantially equivalent. Once a device is cleared through the 510(k) process and becomes eligible as a predicate, it cannot be removed from the pool of available predicates unless it has been banned or declared adulterated or misbranded and pulled from the market. The FDA estimates*

that 29% of the devices that have been cleared either were never marketed or were marketed but are no longer available (FDA, 2010b). Whether that reflects deficiencies in product safety or effectiveness, cost, utility, or competitiveness is not known. Nevertheless, the discontinued (or never launched) products may all serve as predicates for future devices.

Certainly, some medical devices have been removed from the market voluntarily by manufacturers because they have been shown to be unsafe, ineffective, or less effective than other treatments. Allowing such devices to continue to serve as predicates for future devices being cleared under the 510(k) process clearly is not in the best interest of public health and is not a defensible or rational approach for allowing medical devices to enter the market.

(2) Page 74, fourth and fifth paragraphs, and page 75, first paragraph — In its discussion of predicate devices, the committee made the following key observations and findings:

Over the history of the program, systems for tracking and linking 510(k) decisions and predicates have been insufficient (see Chapter 3). As a result, it would be difficult for anyone to trace back the chain of predicates leading to the preamendment device in connection with a device currently on the market. Given that circumstance, the committee finds it important to note that a fundamental difference exists between the 510(k) and PMA pathways. In reviewing a PMA, the FDA must ask, Is this device reasonably safe and effective for its intended use? The 510(k) review asks, Is this device substantially equivalent to some other device whose safety and effectiveness may never have been assessed?

Finding 4-1 The 510(k) process determines only the substantial equivalence of a new device to a previously cleared device, not the new device's safety and effectiveness or whether it is innovative. Substantial equivalence, in the case of a new device with technologic changes, means that the new device is as safe and effective as its predicate.

Finding 4-2 Current 510(k) decisions have been built on a chain of predicates dating back to devices on the market in 1976. Because data systems in the FDA are inadequate, the agency does not have the ability to trace the supporting decisions.

We agree with the committee's observations and findings, which identify the central flaws in the 510(k) process.

(3) Page 75, second paragraph under "**Pushing the Limits of Predicate**" — The committee described the following practice of "split" predicates:

The FDA has cited the practice of multiple and "split" predicates as important challenges in the 510(k) review process (FDA, 2010b). 510(k) submissions that use split predicates combine two or more predicates: one or more predicates for claiming intended use and one or more for claiming technologic characteristics. Split predicates have been used for a variety of devices, including devices with incremental changes.

The practice of allowing split predicates represents a misuse of the definition of substantial equivalence that was established under the 1990 SMDA. The FDA should never have allowed this practice under the 510(k) process and should immediately disallow it.

(4) Page 75-78, "**Key Regulatory Terms**" section — Regarding the terms "intended use" and "indications for use," the committee made the following observations and finding:"

The determinations of "intended use" and "indications for use" are critical elements in the 510(k) process because they directly affect the determination of substantial equivalence (see Figure 4-1). To continue through the 510(k) process, a new device must have the same intended use as its predicate. However, a device is not required to have the same indications for use as the predicate (FDA, 2010b) … It is important to note that terms intended use and indications for use were developed for other regulatory purposes but have been adapted by CDRH to be used as part of the substantial-equivalence decision-making process of the 510(k) review (FDA, 1997).

Finding 4-3 The key regulatory terms intended use and indications for use are poorly defined and are susceptible to varying interpretations that lead to inconsistency in decision-making and create confusion among FDA staff, industry, Congress, the courts, and consumers.

We agree with the committee's finding. The FDA's permissive interpretation of the term "same intended use" is among the many problems with the 510(k) process that we have emphasized in the past.[5] The intended use of a device and its labeled indication are not the same. In the absence of a statutory definition of "same intended use," CDRH practice permits a lenient interpretation of this term. The agency has asserted that its "scientific expertise enables it to exercise considerable discretion in construing intended uses."[12] In practice, the FDA has permitted even novel implantable devices to be reviewed and cleared under the 510(k) process. Such lenient interpretations have allowed unsafe and ineffective devices to reach the market.

(5) Page 79, last paragraph — The committee noted the following in its discussion of off-label uses of medical devices in the context of the 510(k) process:

Some devices have multiple potential indications for use. The magnitude of risk associated with some indications for use may be consistent with clearance through the 510(k) process. Others, however, present a greater risk that is more consistent with the requirements of the PMA process. Because of the considerable differences in the burden between 510(k) clearance and the PMA process, including the submission user-fee, data-collection requirements, and time, there is a potential for manufacturers to circumvent PMA of a device for the higher risk indications and instead seek a 510(k) clearance in connection with the lower-risk indications. CDRH has indicated that the practice of omitting higher-risk indications from the proposed labeling of 510(k) submissions to avoid a more intensive PMA review is an area of concern.

The committee's discussion highlights another important flaw in the 510(k) process that can expose patients to unnecessary risk of harm. To correct this problem, the FDA should require that device manufacturers disclose to the agency all known intended indications for any new medical device prior to marketing and impose serious penalties for any manufacturer who violates such a requirement.

(6) Page 86, first and second paragraphs under "**Use of Clinical Data**" — The committee pointed out the following regarding how infrequently the FDA requests clinical data for devices cleared under the 510(k) process:

The use of clinical data in the regulatory review process is defined by the enabling legislation, the regulations, and the FDA's implementation of the legislation and regulations. The agency is able to request clinical data if it determines that the 510(k) submission under review has new technologic characteristics relative to the predicate(s). The clinical data can be requested by the FDA only if necessary to determine that the new device is as safe and as effective as the predicate device(s). Moreover, the agency may not ask for scientific evidence greater than the "least burdensome" to answer the question.

In practice, clinical data play a very small role in the 510(k) process. The GAO found that in FY 2005–2007 about 15% of Class II and Class III 510(k) submissions had new technologic characteristics (GAO, 2009b). The FDA found that only 8% of 510(k) submissions for non–in vitro diagnostic devices contain clinical data, and of those only 11% reference a predicate for which clinical data was provided.

The FDA should seek new legislative authority allowing it to expand the circumstances under which it can request clinical data for Class II and III devices prior to marketing. This would be particularly important for devices that are intended to be life-sustaining, life-supporting, or implanted.

F. Chapter 5 — POSTMARKETING SURVEILLANCE, COMPLIANCE, AND ENFORCEMENT

(1) Pages 99-103 — Regarding the FDA's current postmarketing surveillance activities, the committee noted the following limitations, among others:

> *It is important to note that for most of the programs discussed below there is no reliable information about the number of devices (referred to as the denominator) on the market in clinical use. The lack of denominator information limits the ability to analyze potential safety concerns… When a medical problem is suspected to have occurred in association with the use of a medical device, a bioengineer or risk manager may or may not be available to assist in the assessment of the role of the device…In addition, the onset of some medical problems [related to a device] may be delayed, and the person using the potentially problematic device may no longer be a patient of a healthcare facility that is legally required to file a [medical-device report (MDR)].*
>
> *Physicians increasingly use higher-risk devices, including implantable devices, in their offices where there is no legal requirement for them to report adverse events and device failures to the FDA. Voluntary reports made by healthcare providers have always made up a very small fraction of the reports received by the FDA …*
>
> *… Most initial reports of adverse medical events or device malfunctions lack critical information about the patient's medical history…*
>
> *The timeliness of the FDA review of MDRs is also problematic. Fewer than one-third of MDRs were reviewed for the first time within 30 days, and fewer than half were reviewed within 60 days in every year from 2003 to 2007. Documentation of the reviews is also inconsistent, and this makes it difficult to track the agency's response to a specific event. Moreover, the FDA Office of Compliance does not link inspections to the adverse event that may have triggered them …*
>
> *… [the FDA's] screening [of MDRs] is made more difficult by the low signal-to-noise ratio, the MDR reviewers' narrow experience with new technology, the absence of input to the reviewers by premarket staff more familiar with the device, and the sheer volume of reports, which exceeds the capacity of the current system (GAO, 2009b; IOM, 2011).*

Based on these limitations, the committee made the following key findings:

> ***Finding 5-1 The FDA's current postmarketing surveillance system relies on manufacturers and healthcare facilities to collect information, to investigate, and to make mandatory reports.***

Voluntary reporting of adverse events and device malfunctions depends on patients, caregivers, and healthcare providers to identify them, associate them with medical devices, and to submit reports.

Finding 5-2 The inadequacy of the current postmarketing surveillance system and the resulting lack of data make it impossible to confidently draw broad conclusions about the safety and effectiveness of products that are on the market.

Finding 5-3 Data collected with the current postmarketing surveillance system is not systematically integrated into the premarket review process.

We agree with the committee's findings. Like the 510(k) process, the FDA's current postmarketing surveillance system is broken and needs a complete overhaul in order to better protect the public health. The agency must implement a more robust and useful postmarketing surveillance system so that it can identify safety problems with medical devices more promptly.

(2) Page 106, "**Section 522 Surveillance**" section, and page 107, second paragraph — The committee observed the following regarding the FDA's use of surveillance under § 522 of the FFDCA:

Section 522 of the FFDCA is a discretionary tool that allows CDRH to require manufacturers to perform specified postmarket clinical studies of Class II and Class III products (Gross and Kessler, 1996). Such studies are justified when device failure is likely to cause serious health consequences, if the device would be implanted for more than a year, or if it is a life-sustaining device used outside a health facility. A Section 522 study can be used as a condition of clearance for a Class II device that is expected to have substantial use in pediatric populations …

CDRH appears reluctant to require Section 522 studies. Only 34 current orders are in progress, primarily in orthopedics (IOM, 2011). Underuse of Section 522 studies has been a persistent problem (Kessler, 2010).

Based on these observations, the committee made the following finding:

Finding 5-4 Several tools, such as device tracking and Section 522 surveillance studies, are available to the FDA to improve postmarketing surveillance, but they are used only sparingly.

As with the FDA's inadequate use of its judicial and administrative enforcement powers in response to safety concerns about marketed devices, the committee correctly has identified the failure of the FDA to utilize one of its already available authorities to require surveillance studies under § 522 of the FFDCA.

G. Chapter 6 — EXTERNAL FACTORS THAT AFFECT THE MEDICAL-DEVICE REGULATORY SYSTEM

(1) Pages 119-124, "**The Growing Number and Complexity of Medical Devices**" section — The committee identified the following external factors that have had a significant impact on the medical-device regulatory system:

> *The number of types of medical devices also has grown. The FDA uses product codes to identify generic categories of devices. The product codes are organized by 16 medical specialties (for example, cardiovascular, general and plastic surgery, and orthopedic), and the medical specialties are listed in the Code of Federal Regulations. From 1990 to 2009, more than 1,000 product codes were added (see Figure 6-2).*
>
> *In addition to the increase in 510(k) submissions to CDRH and the greater variety of types of products that CDRH must review, submissions have become longer and more detailed. As shown in Figure 6-3, the average number of pages per 510(k) submission in 2008 was more than 7 times the number in 1983 …*
>
> *The technologic complexity of medical devices has increased substantially over the past 35 years as well… Examples of new technologies in medical devices are software (incorporated in medical devices and as stand-alone medical devices), nanotechnology, and medical robotics. The evolution (and revolution) of science and technology creates many challenges related to the regulation of medical devices …*
>
> *Multiple predicates and split predicates are cited in over half the 510(k) submissions (FDA, 2010a). In general, multiple and split predicates are used in 510(k) submissions for new devices that are more complex than the predicates …*
>
> *Combination products are therapeutic and diagnostic products that combine drugs, devices, and biologic products (FDA, 2008). As new technologies emerge and older technologies evolve, combination products are increasingly complex. Over the last decade, it has been increasingly common to enhance the performance of medical products by using multiple products together.*

On the basis of these identified factors, the committee made the following finding:

> ***Finding 6-1 Medical-device technologies have evolved rapidly and devices have become increasingly complex since the 1976 Medical Device Amendments.***

We agree with the committee's finding. The increasing complexity of medical devices over the past 35 years, combined with the previously noted deficiencies of the 510(k) process and lack of a comprehensive quality assurance program to assess the 510(k) process on a continual basis, has created circumstances where the likelihood of patients being harmed by unsafe and ineffective medical devices is higher than ever. Because of the increasing complexity of medical devices, the problems that result from the deficiencies in the 510(k) process are becoming more pronounced. Recent examples of devices cleared under the 510(k) process and subsequently shown to be unsafe include multiple non-absorbable synthetic mesh products used for transvaginal repair of pelvic organ prolapse,[6] the Axxent FlexiShield Mini,[13] and the DePuy ASR 300 Acetabular Cup System.[14] Patient harms that resulted from these devices could have been prevented if appropriate clinical data regarding their safety and effectiveness had been obtained prior to their being marketed.

(2) Pages 124-131 — The committee reported the following in its discussion of the increasing use of software in medical devices cleared under the 510(k) process:

> *Manufacturers are increasingly using software in their medical devices. An analysis by Fu showed that a milestone was reached in 2006: since then, over half the medical devices on the market have relied on software in some way (IOM, 2011) …*
>
> *Pfleeger et al. (2002) have written extensively on how software is different from hardware. The authors identify three key characteristics of software that make it different from hardware:*
>
> - *Software developers are overoptimistic. Careful empirical studies have shown that software developers, particularly testers, often assume that they have found the last problem in the software under scrutiny. That is, they commonly stop looking once they find a problem, not recognizing that other problems remain …*
> - *Software is discrete, not continuous. Unlike hardware, software is extremely sensitive to small errors. Off-by-one errors, negligible in hardware, can result in huge changes in software …*
> - *Software is immature and subject to rapid change …*

On the basis of these software characteristics, the committee made the following findings:

> ***Finding 6-2 Manufacturers are using increasing amounts of software in devices and as devices; the increase is expected to continue. Software offers many benefits over hardware, including flexibility, ease of change, and the possibility of use in other devices.***

Finding 6-3 Software is responsible for an increasing number of recalls. There are insufficient data, however, to determine whether the increase reflects the increasing proportion of software in medical devices or a new and different set of problems and vulnerabilities.

Finding 6-4 Software is different from hardware and therefore requires a different kind of evaluation.

The use of software in medical devices is just one more factor that has contributed to the increasing complexity of medical devices.

In summary, the committee's insightful and compelling report identified many inadequacies and flaws in the FDA 510(k) process for clearing medical devices. We completely agree with the committee's main conclusion that this process is broken and cannot be fixed. In particular, the committee found that the legal standard used by the FDA for clearance of medical devices under the 510(k) process — "substantial equivalence" to a predicate device already on the market — fails to ensure that devices are safe and effective. We strongly endorse the committee's primary recommendation that the current FDA 510(k) clearance process "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."

It is crucial that the FDA not disregard this report, but instead moves expeditiously to implement the committee's recommendation, including seeking new statutory authority, when necessary, in order to protect the American public from unsafe and ineffective medical devices.

Thank you for the opportunity to comment on the report.

Sincerely,

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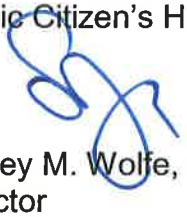

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