Written Statement
Ralph F. Hall
Professor of Practice
University of Minnesota Law School

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A Critical Balance: FDA and the Reform of the Medical Device Approval Process

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Good afternoon, my name is Ralph F. Hall. I appreciate this opportunity to speak to this committee on these important medical device matters affecting patients, physicians, innovation and jobs. I am here to provide an overview of the medical device regulatory system, with particular focus on how the medical device regulatory system assesses product safety and effectiveness. In addition, I will discuss research I and others have done into the safety of 510(k) products.

I want to be clear that I am here speaking in my personal capacity and not on behalf of the University of Minnesota or any other entity.

Background and Disclosures

To start, I serve as Professor of Practitioner at the University of Minnesota Law School where I concentrate my teaching, research and writing in the area of FDA law and compliance matters. In addition, I am part time Counsel at the law firm of Baker & Daniels where I work with clients on a variety of FDA matters and also provide counsel to a national 510(k) coalition. Finally, I serve as CEO at MR3 Medical LLC – a four person start-up medical device company working on a new technology for cardiac rhythm devices generally regulated under the PMA process.

I. Medical Device Regulatory Overview

a. Medical Devices are Significantly Different than Drugs

Many commentators simply compare drug regulation and device regulation. When differences between these systems appear, as they do, these commentators assume that there is some problem. It is absolutely critical to understand that there are important differences between drugs and devices that mandate some different regulatory approaches. These differences include:

- Drugs have a systematic effect on the body. A cardiovascular drug, for example, will also circulate throughout the body and potentially impact the liver, kidneys, muscles, lung, brain, etc. The vast majority of all devices do not have any systemic effect. Thus testing issues and needs are fundamentally different between drugs and devices.
- Medical device development is an iterative process with substantially shorter life cycles. That is not the case with drugs. Drug life cycles cover several decades while device life cycles are often measured in months. Also, drugs do not have the iterative development process found in devices. Any molecular change in a drug creates a new molecule and a whole new set of issues and questions. Most iterative changes to a device (making a catheter longer, for example) do not create new therapeutic issues.
- Essentially all drugs are the actual therapy. Many devices are actually a tool by which a physician delivers therapy, not the therapy itself. For example, a scalpel is a tool by which a medical intervention is performed. In such cases, FDA primary focus should be on whether the tool is performing as required, not whether the therapy such as an appendectomy (a physician decision) is effective.
- Engineering, design controls, human factors and material sciences are much more important to devices than to drugs. As detailed below, most post market safety issues with medical devices involve engineering, design, materials and manufacturing issues, problems not discoverable through clinical risks. Available data indicates that this is a different pattern from drugs. This difference in risk should impact premarket requirements.
- Devices span a much greater risk profile than drugs. While essentially all drugs pose some systemic questions that is not the case with devices. There is a world of difference between the risk/benefit of an implantable neuromodulator and that of a crutch. This huge risk spectrum mandates phased regulation of medical devices.
- There is incredible product differentiation within medical devices. Medical devices include diagnostic tools that never touch a patient, multimillion dollar pieces of capital equipment such as CT scanners, simple tools like a scalpel or bandaid and complex implantable devices such as an ICD.

- Device regulation includes robust and broad quality system requirements (often referred to as QSR requirements).

The overall impact of these differences is that device regulation needs different premarket requirements, a risk based approach to regulation and an emphasis on quality systems.

b. Device regulatory overview

By statute and regulation, all medical devices, regardless of risk classification, are to have a "reasonable assurance of … safety and effectiveness" before they are marketed.[1] What differs is the method by which FDA and other stakeholders assess whether there is such assurance of safety and effectiveness for different classes of device.[2] These different ways to provide this assurance of safety and effectiveness and the complex language and statutory systems for medical device regulation can lead to inadvertent confusion and misunderstanding. However, all products of whatever risk classification must provide this reasonable assurance of safety and effectiveness.[3]

Because medical devices differ so much – from a tongue depressor to a multimillion dollar robotic surgical system – one regulatory approach does not fit all. To address this, Congress created a three tier regulatory structure.

- Class I devices are the simplest, lowest risk devices. These include crutches, tongue depressors and scalpels. These products usually do not go through a premarket review and are generally referred to as Class I exempt.
- Class II devices are medium risk products such as angioplasty catheters. Class II devices generally go through the 510(k) system.
- Class III devices are the highest risk devices and include heart values and pacemakers. These products reach market through the PMA process.[4]

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1 21 U.S.C. §393(b)(2)(C)

2 It goes without saying that all therapeutic products have some risks. The objective is to ensure a positive risk/benefit for each product.

3 Ensuring patient access to beneficial products is also critical. As such, FDA is also charged with promoting product innovation. While the focus of my comments is on the safety aspects of the device regulatory system, one cannot forget the importance of making innovative products available to physicians and patients.

4 This is a general description. Some higher risk Class I devices must go through the 510(k) system and some higher risk Class II products require a PMA. There are also some other pathways to market including the HDE process and the rarely used PDP system. For our purposes these alternative pathways are not relevant.

Each device class, with some overlaps, uses a different method to provide assurances of safety and effectiveness.

Class I products are those for which "general controls" are "sufficient to provide reasonable assurance of the safety and effectiveness of the device".[5] General controls can include, as appropriate, manufacturing controls, labeling, quality systems, etc.

Class II products are those for which general controls by themselves are not sufficient but for which "special controls" do provide a reasonable assurance of safety and effectiveness. These products use a different, multipronged system to provide the reasonable assurance of safety and effectiveness. Specifically, Congress provided that a Class II device is:

> A device which cannot be classified as a Class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance [of safety and effectiveness], including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance.[6]

As mandated by Congress Class II devices generally must receive clearance under the 510(k) system described in more detail below and as part of that process must satisfy both special controls and general controls. 510(k) submissions can include clinical data, bench testing, labeling, reports on prior investigations, etc.

The 510(k) system (described in more detail below) generally requires a product to establish that it is "substantially equivalent" to a predicate 510(k) device. Substantial equivalence is more than a physical comparison of one device to another. 510(k) products must also meet all special controls, all applicable standards and QSR requirements. FDA has the authority under the 510(k) system to request a wide variety of data, including clinical data, bench testing, proposed labeling, and material information, as part of its review of a 510(k) submission.[7] This submission explicitly includes a variety of safety and effectiveness information.[8]

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5 21 U.S.C. § 360c(a)(1)(A)(i).

6 21 U.S.C. § 360c(a)(1)(B).

7 21 C.F.R. §§ 807.87, .90, .92 and .93 set forth more details about the content and format of a 510(k) submission.

8 See, for example, 21 C.F.R. § 807.92(c)(3).

Class III products must go through the PMA process.[9] This often includes clinical testing and submissions include detailed manufacturing information, labeling, bench test data, etc. FDA reviews this data for safety and effectiveness.

It is important to understand that there are a number of other systems that also impose safety and effectiveness controls on products as part of an integrated system to provide a reasonable assurance of safety and effectiveness. For example, the QSR system[10] requires design controls to help ensure a safe and effective design. There are also product and adverse event trending requirements, reporting requirements, etc. In addition, FDA has the authority to require post market testing on higher risk devices (including specifically Class II/510(k) products).[11] There are also general labeling requirements including 21 U.S.C. § 352(f) which mandates that a product labeling include "adequate directions" for safe use.

II. The 510(k) system includes safety and effectiveness considerations

The 510(k) system has been the focus of recent attention. The 510(k) system does consider safety and effectiveness. Stated differently, current FDA authority gives the agency multiple pathways to keep an unsafe 510(k) product off the market, require whatever testing or data is needed to establish safety and effectiveness and remove unsafe products from the market.

From the beginning, Congress intended for the 510(k) system (and the substantial equivalence part of that process) to include safety and effectiveness determinations. As FDA itself explained to the IOM committee in March 2010, Congress intended the 510(k) substantial equivalence standard to be flexible in order to assure safety and effectiveness. The 510(k) legislative history states:

> The [Congressional] committee believes that the term [substantial equivalence] should be construed narrowly where necessary to assure the safety and effectiveness of a device but not narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness.[12]

Note the specific linkage of the substantial equivalence determination to safety and effectiveness.

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9 21 U.S.C. § 360e.

10 QSR requirements are generally found in 21 C.F.R. § 820.

11 21 U.S.C. § 360l. 21 U.S.C. § 360l(a)(1)(A) explicitly includes Class II devices within the group of products subject to so-called "522 orders."

12 See FDA's presentation to IOM available at http://www.iom.edu/Activities/PublicHealth/510KProcess/2010-MAR-01.aspx.

In order to see how the Class II/510(k) system ensures an assessment of safety and effectiveness, one must understand the process from the start. The 510(k) process actually begins before the first product is reviewed. By statute, FDA is obligated to classify each product type into Class I, II or III. This classification process includes expert advisory panels, assessment of data and an opportunity for stakeholder input.[13] The purpose of the classification process is to determine which oversight system is best positioned to provide assurances of safety and effectiveness. The product classification is based on safety and effectiveness considerations as confirmed by the implementing regulation which states:

> b) **In determining the safety and effectiveness of a device for purposes of classification**, establishment of performance standards for Class II devices, and premarket approval of Class III devices, the Commissioner and the classification panels will consider the following, among other relevant factors:
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> > (1) The persons for whose use the device is represented or intended;
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> > (2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
> >
> > (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
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> > (4) The reliability of the device (emphasis added).[14]

Further, by statute, if a product is implantable or is used to support or sustain human life, the default classification is Class III/PMA unless the agency and classification panel specifically determine that the Class II/510(k) process is sufficiently robust and that Class III/PMA systems are not necessary to provide reasonable assurance of safety.[15] Thus, before any device is even eligible for 510(k) review, FDA, in concert with expert classification panels, has made a determination that the Class II/510(k) system provides an adequate assurance of safety and effectiveness for that product type.[16] Therefore, every 510(k) product type has been assessed and

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13 21 U.S.C. § 360c(c) and (d).

14 21 C.F.R. § 860.7(b).

15 21 U.S.C. § 360c(c)(2)(C).

16 As GAO and a number of commentators have noted, FDA is delinquent in classifying 26 out of, I believe, approximately 1,800 product types. These products continue to be reviewed under the 510(k) system. FDA is currently in process of rectifying this situation and completing the classification of these remaining products.

it has been determined that the 510(k) system provides the adequate assurance of safety and effectiveness.

Once classified, the 510(k) system uses the concept of "substantial equivalence" as a method to assess safety and effectiveness.[17] The policy behind the 510(k) system is that once is has been determined that a product type is safe and effective for its intended use, future products that are "substantially equivalent" to the initial product and which meet all other regulatory requirements are likewise safe and effective. Substantial equivalence is more than a physical comparison of one product to another.

The 510(k) submission provides the information to FDA by which it can determine that the safety profile of the new product meets the established safety profile of the prior (or predicate) device, all special controls or similar requirements have been met and that the product is otherwise safe and effective for its intended use. The submission specifically includes safety information.

For example, 21 C.F.R. § 807.92(c)(3) states that a 510(k) summary must include:

> The conclusions drawn from the nonclinical and clinical tests that demonstrate that the device is as safe, as effective, and performs as well as or better than [the predicate device].

21 U.S.C. § 360c(i)(3)(A) requires a 510(k) submission to include adequate information respecting the safety and effectiveness of the device and/or to make that information available. Under 21 U.S.C. § 360c(i)(3)(B), this summary shall include detailed information regarding adverse health effects relating to the product and this information shall be made available to the public.[18]

In addition to data submission requirements, Congress has given FDA another powerful tool to ensure product safety and effectiveness. The 510(k) system makes explicit use of "special controls" to ensure safety and effectiveness and any 510(k) product must satisfy all special control requirements. Under 21 U.S.C. § 360c(a)(1)(B), special controls are explicitly used to provide a reasonable assurance of safety and effectiveness. Special controls can include clinical

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[17] In reviewing 21 U.S.C. § 360c – the key statutory section relating to Class II/510(k) devices – one can see that Congress used the term "safety" with regard to Class II/510(k) products more than 17 times by my count. One can only wonder why Congress would discuss safety so many times unless Congress intended for the 510(k) to consider safety and effectiveness.

[18] One is hard pressed to argue that congress intended FDA to have this safety and effectiveness information and then mandated that FDA ignore that data in making 510(k) clearance decisions.

data requirements, performance standards, patient registries, guidance documents, etc. Any new product must comply with all applicable special controls. These special controls are used in addition to physical identicality to establish safety and effectiveness.

Products can and usually do evolve over time. The "substantial equivalence" process is designed to subject any new product use or technology to an explicit safety and effectiveness review. Congress specifically required FDA to assess new intended uses and new technologies for safety and effectiveness.[19]

There is, of course, the concern that changing information or new data may call into question prior classification decisions or special controls. Congress anticipated this concern and explicitly established reclassification processes under 21 U.S.C. § 360c(e) that FDA can use (and any stakeholder can request) in the event of new information. This reclassification process can address any new information and either up classify or down classify a device type as the data directs. Any down classification from Class III to Class II requires a determination that Class II special controls provide a reasonable assurance of safety and effectiveness. Likewise, FDA can create new or enhanced special controls under 21 U.S.C.§ 360c(a)(1(B) to address new safety or effectiveness issues.

Congress has provided FDA with other tools to ensure that an unsafe Class II product does not reach the market. For example, FDA has the authority to ban unsafe devices,[20] and ensure that the product labeling permits safe use.[21] Any product that has been removed from the market "at the imitative" of FDA or has been found to be misbranded or adulterated by a court cannot be used as a predicate to a later product.[22] This is one method by which a "bad" predicate cannot be used for future products. Other tools include the ability to develop new or enhanced special controls and to require additional data to be submitted.

While the term "substantial equivalence can sound like merely a physical comparison of one product to another, an understanding of the overall 510(k) system demonstrates that much more than physical identity is needed to be cleared for marketing. Before a product can be deemed to

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19 21 U.S.C. § 360c(i)(1). Note that new technology is broadly defined to ensure that product changes are reviewed for safety and effectiveness. 21 U.S.C. § 360c(i)(1)(B).

20 21 U.S.C. § 360f(a).

21 21 U.S.C. § 352(f). Even if a product is "substantially equivalent" to another, if it cannot be labeled so that it can be used safety, the product is misbranded and distribution of such a product triggers civil and criminal liability.

22 21 U.S.C. § 360c(i)(2).

be "substantially equivalent" and the product legally marketed the system requires, among other requirements:

- Product classification into the 510(k) system based on safety and effectiveness assessments
- Compliance with special controls explicitly intended to provide assurances of safety and effectiveness
- Compliance with all applicable standards and guidances
- Assessment of any new intended uses or new technology for safety and effectiveness
- Submission of safety and effectiveness data and adverse health information
- Compliance with all applicable general controls
- Compliance with QSR requirements

As such, FDA has multiple avenues to assess and address any safety or effectiveness issues.

III. Key Examples

I will now apply the 510(k) system to the three key product situations to demonstrate that, in each case, FDA has the authority to assess safety and effectiveness.

a. The New Product

There are situations in which a product is developed for which there is no predicate. Normally, these products are automatically, by application of statute, classified as PMA products.[23] Unless there is an actual reclassification, these products go through the PMA process and so there is no question about the robustness of the 510(k) process.

However, such a product may well be a medium risk product and so best regulated as a Class II/510(k) product. In these cases, the product can be classified as a Class II/510(k) product pursuant to the "de novo" process under 21 U.S.C. § 360c(f)(2). This classification process explicitly considers whether the product can be safely regulated under Class II systems including special controls.

[23] 21 U.S.C. § 360c(f)(1).

As such, no "new" product can be regulated under the 510(k) system unless FDA has made an explicit determination that the 510(k) system provides adequate assurances of safety and effectiveness.

b. Changes to an "old" product

The next fact pattern involves an existing product, already in the Class II/510(k) system, to which the company is making some change. This can be a new intended use or some change in technology. In each case, the change in the product must be explicitly assessed for safety and effectiveness.[24] The product cannot be cleared if the product raises some new issue of safety or effectiveness.[25]

Remember that one of the core concepts of the 510(k) system is that once safety and effectiveness has been determined, like products can establish safety and effectiveness based on the prior assessment. Of course product changes can challenge this concept and so Congress as decreed and FDA has insisted that any change in the use of the product or the technology (broadly defined) must be assessed to ensure safety and effectiveness. Thus, Congress and FDA have assured that product iterations or changes will be assessed for safety and effectiveness.

c. Continued marketing of an "old" product

The final challenge is the one that seemed to bother the IOM committee and others the most and this is the old product that hasn't changed.[26] Some seem to believe that these "old" products have never been assessed for safety and effectiveness and that FDA is bound to clear any such product without considerations of any safety or effectiveness issues. This is simply not the case.

FDA has multiple authorities to keep an unsafe 510(k) product – even if literally identical to an old product – off the market.

To start, all products have been assessed for safety and effectiveness issues through the classification process.[27] Even if the product existed before 1976, it has been specifically

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24 21 U.S.C. § 360c(i) and 21 C.F.R. § 807.

25 FDA's internal processes and flow charts reinforce the fact that any change in intended use or technology is assessed for safety and effectiveness. There is a "not substantially equivalent" ("NSE") determination if there is some new question of safety or effectiveness.

26 This includes situations in which the old, unchanged, feature of the product presents some new safety or effectiveness issue.

27 I recognize that a few products (some number less than 26 out of approximately 1,800 product codes) have not completed this process. As many others have previously said, this process must be completed. FDA is currently in the process of doing so.

assessed and a determination made that products of that type can be regulated under the Class II/510(k) system for safety and effectiveness.[28] Just because a product was on the market before 1976 does not mean that it is part of the 510(k) system.

The related question is what happens if new information is developed on an "old" product subsequent to its classification. First, FDA has access to such information through any number of sources. Importantly, Congress has decreed that the company must include adverse health information in its 510(k) submission.[29]

Once such information comes to FDA's attention, FDA has any number of approaches to prevent an unsafe product from being cleared via the 510(k) system. Examples of these tools include:

- Creating new or enhanced special controls to mitigate or eliminate the newly discovered risk[30]
- Reclassifying the device into Class III[31]
- Creating or adopting new guidances or standards
- Requiring new labeling to mitigate or eliminate the issue (or concluding that such improved labeling would not be effective and thus the product is misbranded)[32]
- Imposing post market obligations[33]
- Banning the device[34]
- Utilizing QSR requirements to address the issue[35]

Thus, each product type is reviewed for safety and effectiveness issues at the time of initial classification. Post classification, FDA has multiple statutory and regulatory authorities available to prevent an unsafe product from being cleared.

Congress did not create – and FDA is not implementing – a regulatory system under which FDA has no choice but to clear an unsafe device.

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28 See 21 U.S.C. § 360c(c) and (d) and 21 C.F.R. §§ 807 and 860 for more details.

29 21 U.S.C. § 360c(i)(3).

30 21 U.S.C. § 360c(a)(1)(B).

31 21 U.S.C. § 360c(e).

32 21 U.S.C. § 352(f).

33 21 U.S.C. § 360l.

34 21 U.S.C. § 360f.

35 21 C.F.R. § 820.

IV. FDA in fact makes safety and effectiveness determinations in product clearances

How the 510(k) system actually works is best demonstrated by looking at actual product clearances. In many cases, FDA specifically indicates in the clearance documents that the product in question is safe and effective for its intended uses.

For example, Via Biomedical, Inc.'s Stent Graft Balloon Catheter has been determined substantially equivalent and cleared for market distribution.[36] Included in the 510(k) summary was the following:

> The Stent Graft Balloon Catheter underwent mechanical, performance, and Biocompatibility testing to verify that the device functions in a ***safe*** **and** ***effective*** manner. The results of the tests provide reasonable assurance that the device has been designed and tested to assure conformance to the requirements for its indications for use.[37] (emphasis added).

Becton, Dickinson and Company's (Becton) BD Flu+ Syringe was cleared for market on July 2, 2009. As part of its submission, Becton expressly indicated that "[d]esign [v]erification tests were performed based on the risk analysis performed, and the results of these tests demonstrate that the BD Flu + Syringe performed in an equivalent manner to the predicate device and is *safe* and *effective* when used as intended.[38]

Likewise ArthoCare's Bone Cement Opacifier was cleared under 510(k) after the FDA confirmed that "the performance testing and device comparison demonstrated that the subject device [was] substantially equivalent to the predicate device, ***and*** **is safe and effective for its intended use**.[39] (emphasis added).

There are numerous other examples of 510(k) submissions that have been included safety and effectiveness data and have been assessed by FDA for safety and effectiveness. A few examples include the Master Healthcare's Easy Touch Insulin Syringe,[40] ZOLL Circulation's Central

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[36] 510K Summary from Via Biomedical, Inc., on the Stent Graft Balloon Catheter (May 29, 2009), http://www.accessdata.fda.gov/cdrh_docs/pdf9/K091624.pdf.

[37] *Id.* (emphasis added).

[38] 510K Summary of Safety and Effectiveness from Becton, Dickinson and Company on the BD Flu+ Syringe (Jul. 2, 2009), http://www.accessdata.fda.gov/cdrh_docs/pdf9/K091377.pdf.

[39] 510K Summary from Becton, Dickinson and Company on BD Flu+ Syringe, http://www.accessdata.fda.gov/cdrh_docs/pdf4/K042947.pdf. The device was not found to be *as* safe as the predicate, but there was an independent assessment. The device was both substantially equivalent to the predicate as well safe and effective.

[40] 510K Summary from Masters Healthcare on the Easy Touch Insulin Syringe (May 14, 2009) http://www.accessdata.fda.gov/cdrh_docs/pdf9/K091474.pdf.

Venous Catheter and Thermal Regulating System[41] and Medtronic's Cardiopulmonary Centrifugal Blood Pump.[42] All of these submissions included performance data specifically relating to the safety and effectiveness of the device as part of the 510(k) clearance.

As these and other examples demonstrate, FDA in fact considers safety and effectiveness in product decisions.

Furthermore, in numerous presentations, guidance documents and public statements, FDA has said that the 510(k) system includes safety and effectiveness protections.

In summary, it can be seen that products going through the 510(k) system are assessed for safety and effectiveness beginning with the initial classification process. FDA has a variety of tools including special controls to ensure product safety. Congress did not create a system by which literally thousands of devices have been cleared without protecting patient safety.

V. Medical Device Safety Study Summary

The actual safety of medical devices is, of course, of prime importance to patients, physicians and other stakeholders.

There have been several studies of medical device safety (or reasons for medical device problems) over the past two years. These include a study I have done (and presented to the IOM 510(k) committee), a study by Dr. William Maisel (also presented to the IOM 510(k) committee) and a recent report by FDA itself.

In my view, these studies, individually and together, support two key conclusions:

(1) there is no evidence of any overall systemic issue with the safety of 510(k) products and

(2) the primary cause of medical device safety recalls are quality system issues, not a lack of premarket clinical testing. I will also note that the IOM 510(k) committee itself also found no evidence of a systemic issue with the safety of 510(k) products. The committee has explicitly stated: "The committee is not suggesting

[41] 510K Summary from ZOLL Circulation for Venous Catheter and Thermal Regulating System (Oct. 12, 2010), http://www.accessdata.fda.gov/cdrh_docs/pdf10/K101987.pdf.

[42] Summary of Safety and Effectiveness from Medtronic for the Cardiopulmonary Centrifugal Blood Pump (Jun. 21, 2010), http://www.accessdata.fda.gov/cdrh_docs/pdf10/K100631.pdf.

that all, many, or even any medical devices cleared through the 510(k) process and currently on the market are unsafe or ineffective."[43]

My comments will focus on the study I performed assessing the overall safety profile of medical devices approved or cleared by FDA from 2005-2009 by using Class I safety recall data. This research was funded by the Ewing Marion Kauffman Foundation, a private nonpartisan foundation based in Kansas City, MO. Their generous support made this research possible. The Kauffman Foundation has given me complete academic freedom to pursue this research.[44]

This study[45] evaluated Class I (or high risk) recalls of all medical devices, regardless of whether they were approved through the PMA system, cleared through the 510(k) process or were otherwise exempt.

The key conclusions from my research are as follows:

(1) Overall, 510(k) regulated medical devices have an excellent safety profile. Over 99.5% of 510(k) submissions assessed during this study period did not result in a Class I safety recall. Over 99.7% of 510(k) submissions did not result in a Class I recall for any reason relevant to the 510(k) premarket system.

(2) Products approved through the PMA system also have an excellent safety record. Again, greater than 99.5% of PMA or sPMA submissions do not result in a Class I safety recall during the study period.

(3) Very few (less than 9%), Class I recalls during the study period involve possible undiscovered clinical risks. As such, increased preapproval clinical testing would not have any meaningful impact on reducing the number of Class I recalls.

(4) The majority (approximately 55%) of all Class I recalls involve problems or issues that arose after market release and could not be affected by premarket approval systems or requirements. For example, a manufacturing mistake made three years after FDA approval or clearance may trigger a Class I recall.

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[43] See IOM report brief available at http://www.iom.edu/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx.

[44] I want to thank Amanda Maccoux, Mark Jones, Chris Walker and Ron Song - the research assistants at the University of Minnesota Law School - who spent long hours doing the detailed data collection and coding required for this study. Their talents, hard work and dedication are vital to this research and I appreciate all that they did.

[45] An earlier version of this research into the safety of medicals devices through an analysis of safety recalls was presented to the Institute of Medicine committee reviewing the 510(k) system and reviewed with FDA.

However, any premarket requirements such as clinical testing are irrelevant to preventing such a recall.

(5) A very significant majority (over 90%) of all Class I recalls (including both premarket and post-market issues) are directly related to quality system issues (so-called QSR systems[46]). Improved QSR systems will have the greatest effect in reducing the number of Class I recalls.

(6) My study did identify a bolus of Class I recalls in two device types – automatic external defibrillators ("AEDs") and infusion pumps. Any changes to the premarket review process should be targeted to demonstrate problems rather than applied in some random, shotgun way.

(7) Finally, one should not confuse classification for premarket review processes with recall classification. These are very different things and serve very different purposes.

VI. Study Background

The need for the research that I will describe goes back several years when a number of stakeholders started to question the robustness of the 510(k) system. I was particularly struck by the fact that there was no good, objective data to support or refute the assertion that the 510(k) system needed to be changed because of these presumed safety issues.

Given my concerns over the lack of hard data, I commenced a study (with the able assistance of four research assistants) assessing the safety performance of FDA approval processes. To my knowledge, this was the first study designed to systemically assess the safety performance of the 510(k) system.

VII. Study Methodology

This study assessed the overall safety profile of medical devices approved or cleared by FDA from 2005-2009 by using Class I safety recall data.

Class I safety recalls were chosen as the measure of safety as these recalls involve any medical device problem posing any significant risk of serious health consequences to patients and also correctly exclude risks considered as part of the approval or review process. Class II recalls

[46] QSR requirements are intended to provide "cradle to grave" product quality in a closed loop, learning system. QSRs include design input and processes, design validation, product testing, manufacturing controls, process controls, change controls, management review and post-market assessments. See, generally, 21 C.F.R. § 820.

involve generally remote risks to patients and Class III recalls involve minimal or no risk to patients. FDA, not industry, is responsible for assigning the recall classification.

Note that the Class of recall assigned by FDA is independent of the product's device classification. For example, no one would argue that a tongue depressor is a high-risk device or needs a clinical trial. For premarket purposes it is classified as a low-risk, exempt device. However, if the tongue depressor gets contaminated with deadly bacteria because of product tampering or some manufacturing problem there is a significant risk to patients. This would be a high-risk or Class I recall even though for premarket review purposes it is a low risk device.

Using FDA databases, we identified all Class I recalls posted by FDA on public databases during 2005-2009. We first combined all duplicate recalls into one data set of unique or stand alone recalls. (FDA may have several recall announcements and thus there may be multiple data entries for the same issue because of different package configurations, brand names or product sizes).

One hundred eighteen (118) unique recalls were identified. We then coded each recall for a number of factors including regulatory pathway, medical specialty, whether implantable and three letter product code. We also coded each recall with one of thirteen reasons for recalls. Generally speaking, these thirteen recall reasons can be combined into three broad groupings of premarket issues (*i.e.*, something that could, at least theoretically, have been discovered during a premarket review process), post-market issues and miscellaneous (counterfeit and "quack" products). We used FDA websites and publicly available information for this coding.

This study must be assessed in light of the following factors and limitations:

(1) First, we relied entirely upon publicly available data. We did not identify any meaningful errors in this data but did not conduct any structured assessment of the accuracy of FDA's data.

(2) Second, while companies are obligated to report recalls, there may be situations in which the company failed to meet this obligation. We believe that any such missing recalls would tend to be small and not common because of the penalties for non-compliance and the variety of information sources that would disclose any such recall. Importantly, there is no reason to believe that the distribution of the causes of such recalls would be different than the data we had.

(3) Third, we reviewed Class I recalls and not Class II recalls. (FDA defines a Class II recall as a situation in which the problem "might cause a temporary health problem, or pose only a slight threat of a serious nature.) We believe that Class I recalls represent all recalls with any meaningful risk to patients and so represent a valid safety picture. Remember that Class II recalls are for remote risks or low impact problems. Class I recalls represent the majority of actual patient risk and tend to err in the direction of higher rather than lower classification. Risks as low as 1/20,000 have been classified as Class I recalls thus demonstrating the breadth of risks captured by Class I recalls.

(4) Anecdotal review of some Class II recalls indicate (but does not establish) the same general pattern of reasons for recalls between Class I and Class II recalls.

(5) Finally we did not assess any effects of various regulatory systems or actions on patient access to new products, innovation or the economy in general.

We also determined the percentage of 510(k) submissions that resulted in a subsequent Class I recall. The numerator for this calculation is the number of recalls. The denominator is the number of submissions. The denominator for this calculation is a close estimate as there is no direct connection between the date of the submission and the subsequent recall. For example, a recall for a design defect might occur within a month after market release while a recall for a manufacturing error or packaging mistake could occur literally years after approval or clearance.

We determined an annualized number of submissions by taking the average number of submissions for a ten-year period (2000-2009) and annualizing that number. We used this number for all percentage calculations. Those percentages, however, are approximations due to this data challenge.

VIII. Study Results and Data

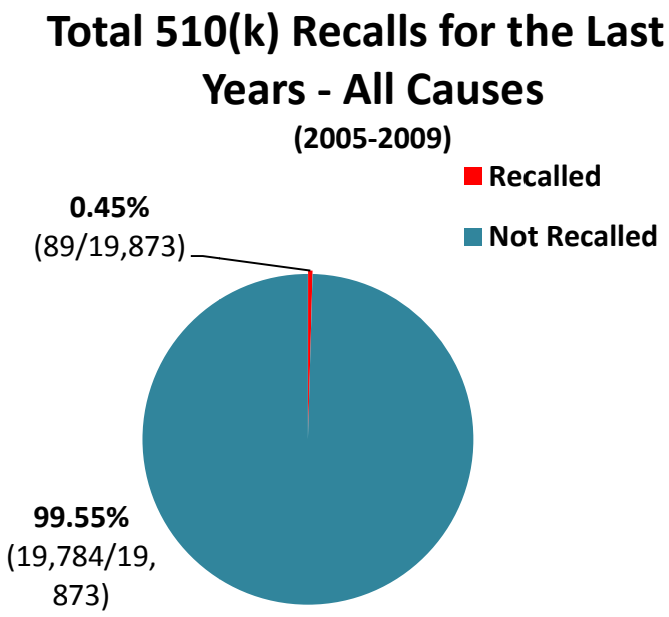
Initially, we looked at the reasons for recalls for these 118 Class I recalls. We determined the reason for the recall by examining FDA's public databases and also reviewing publically available information including physician notification letters and SEC filings. I was responsible for all decisions relating to the reason for recall. I blindly recoded 10% of the recalls and had a complete match with the initial determination of the reason for the recall.

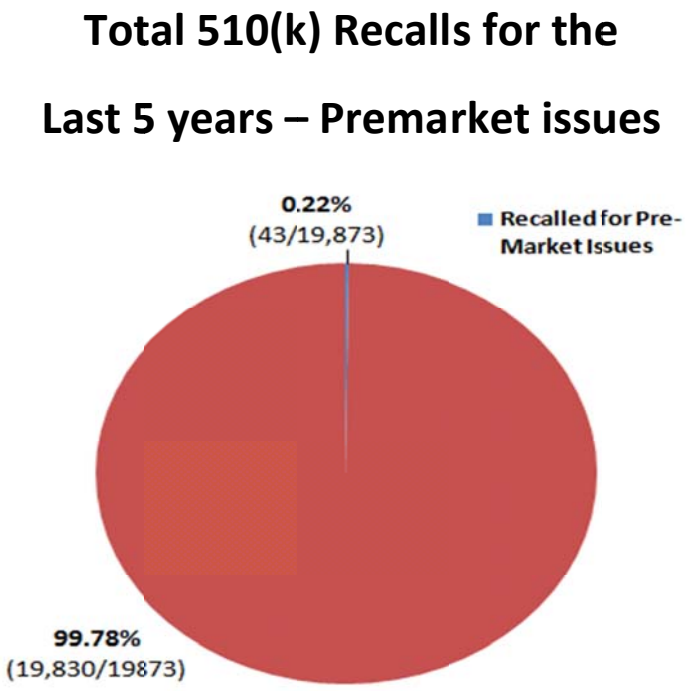
As shown below, the majority of all recalls (approximately 55%) are for post-market issues. For these recalls, no change in the premarket 510(k) or PMA process would affect the recall occurrence or frequency.

	Total Recalls	Recalls for Pre-Market Issues	Recalled for Post-Market Issues	Recalled for Other Issues	Percent of Recalls to Total Recalls
Class I or u/k	7	1 (14.2%)	6 (85.7%)	0 (0%)	5.9%
510(k)	95	43 (45.3%)	46 (48.4%)	6 (6.3%)	80.5%
PMA	16	7 (43.8%)	9 (56.3%)	0 (0%)	13.56%
TOTAL	118	51	61	6	118

As seen below, a very small percentage of 510(k) submissions led to a Class I recall during our study period. The first chart shows the ratio of 510(k) submissions to all Class I recalls and the second chart shows the ratio of 510(k) submissions to Class I recalls related to any theoretical premarket issue.

Based on this data, approximately 99.55% of all 510(k) submissions did not result in a Class I recall for any issue during the study period. More importantly for assessing the 510(k) process, approximately 99.78% of all 510(k) submissions did not result in a Class I recall for any reason related to the premarket process. Stated differently, the maximum theoretical impact of any change in the 510(k) system would be on 0.22% of all 510(k) submissions. This data also demonstrates that additional premarket clinical testing would be ineffective in reducing Class I safety recalls.

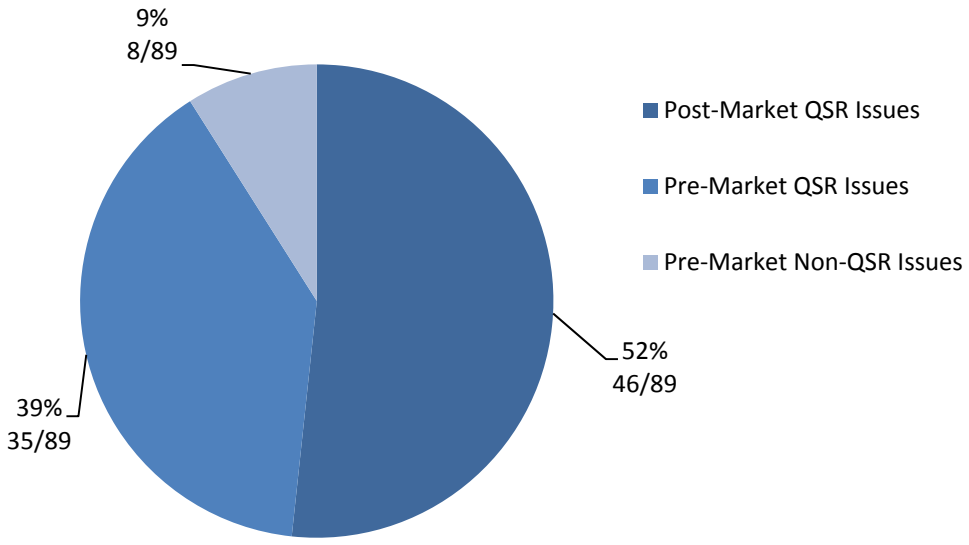

Total 510(k) Recalls for the Last 5 Years - All Causes
(2005-2009)
Recalled
Not Recalled
0.45%
(89/19,873)
99.55%
(19,784/19,873)


Total 510(k) Recalls for the Last 5 years – Premarket issues
0.22%
(43/19,873)
Recalled for Pre-Market Issues
99.78%
(19,830/19873)

Total 510(k) Submissions in 10 years	**39,747**
Average Submissions in 5 year time period	**19,873**
Total 510(k) Recalls for 2005-2009	**89**
Total 510(k) Recalls for Pre-Market Issues for 2005-2009	**43**

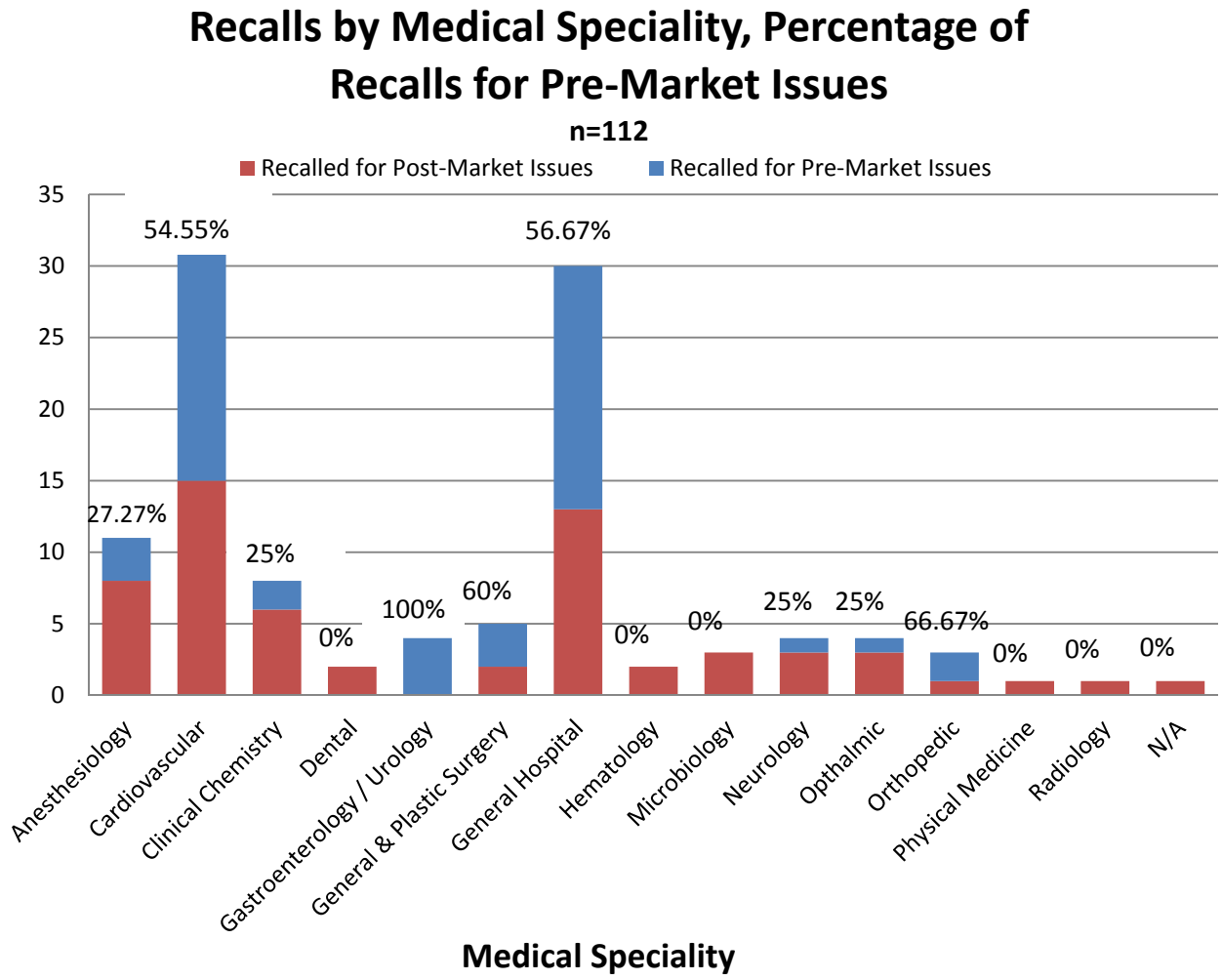
The number of recalls related to premarket issues is most relevant in assessing whether the 510(k) system is adequately addressing patient safety during the review process. This data demonstrates that post-market issues, not premarket processes, should be the focus to improve patient safety.

This conclusion is reinforced when we reviewed the role of quality systems in recalls. As shown below, over 90% of all Class I safety recalls are related to quality system issues and not to other factors such as a lack of clinical trials.



Clearly, this data demonstrates that all stakeholders should concentrate on QSR systems such as design control and bench testing — not the 510(k) submission system — as the most effective way to provide greater patient safety.

We also did sub-analysis by product type and medical specialty. Such analysis can be used to identify concentrations of issues for further investigation by FDA, industry and other stakeholders. As seen below, Class I recalls are concentrated in several product types.



Further analysis indicated that automatic external defibrillators (AEDs) and infusion pumps accounted for 28% of all Class I recalls and accounted for a substantial part of the bolus or recalls seen in the cardiovascular and general hospital categories. Within the past nine months, FDA has triggered new regulatory initiatives for both AEDs and infusion pumps.

Our confidence in our study design and results has been bolstered by subsequent studies by others such as FDA itself, Dr. Maisel and Battelle finding very similar numbers and reasons for Class I recalls.

IX. Study Conclusion

This study demonstrates that very few 510(k) medical device submissions — less than 0.5% — become the subject of a Class I safety recall. Even in this small number of Class I recalls, the majority of Class I recalls involve post-market issues such as manufacturing mistakes, and are focused around two product categories (cardiovascular and general hospital). These recalls involve quality system issues, not premarket issues. Overall, in excess of 90% of all recalls appear to involve quality system issues.

Our study shows that FDA has a very positive safety record in its 510(k) clearance decisions.

X. Conclusion

The current 510(k) system gives FDA substantial authority to clear only products with a reasonable assurance of safety and effectiveness. FDA has multiple tools beginning with initial product classification and extending through special controls and data submission requirements to assess product safety and effectiveness.

Overall, products approved or cleared by FDA have very good safety records. Of course, all stakeholders should always be striving to improve on this already good record. Improvements in QSR (quality systems) offer the greatest potential patient benefit.

Again, I appreciate the opportunity to present to the committee and would be happy to answer any questions.