SUBSTANTIAL EQUIVALENCE REVIEW OF MEDICAL DEVICES

The pilots on our Western rivers steer from point to point as they call it—setting the course of the boat no farther than they can see; and that is all I propose to myself in this great problem. – Abraham Lincoln

Make a tree good and its fruit will be good, or make a tree bad and its fruit will be bad, for a tree is recognized by its fruit. – Matthew 12:33

I. INTRODUCTION

The wide variety of medical devices, and the constant drive to modify them in pursuit of better performance, creates a difficult review problem for the Food and Drug Administration (FDA). How is it possible to apply a risk-based framework that can accommodate the wide heterogeneity of medical devices and their short cycles of iterative improvement, while still providing reasonable regulatory oversight through a predictable process? How is it possible to require an appropriate level of premarket safety and effectiveness data for innovative technology, without unduly inhibiting it from reaching the market?

As it turns out, the 510(k) program based upon “substantial equivalence” review has performed reasonably well at accommodating these conflicting objectives. Approximately 98% of medical devices requiring premarket review reach the market via 510(k) clearance. Taken as a whole, the 510(k) program has proven adaptable to a wide variety of devices, and has allowed meaningful premarket review while fostering robust technological innovation. Under the 510(k) program, the device industry has flourished and allowed for increasingly safer and more beneficial device technology, thus providing a practical demonstration that the 510(k) program is working well.

Certainly, there can be improvements, and I will argue for a reform that I believe would significantly improve its predictability and efficiency. The 510(k) program is often criticized as inherently flawed or as a regrettable but necessary shortcut to an evaluation of “absolute” device safety and effectiveness. As discussed, I reject these views. In fact, as discussed, the 510(k) program has developed into an excellent approach to premarket review of medium risk devices. The use of substantial equivalence as the standard of premarket review has strengths that have not been well articulated. I hope that this paper will add some balance to the discussion.
II. 510(K) REVIEW

The tripartite legal classification structure for medical devices is well known to practitioners in this field.\(^1\) It goes like this:

- **Class I**—devices requiring only postmarket “general controls” (applicable to all classes) to provide reasonable assurance of safety and effectiveness. General controls include: establishment registration and device listing; adulteration and misbranding provisions; reporting of certain adverse events, malfunctions and recalls to FDA; and good manufacturing practice requirements.\(^2\)

- **Class II**—devices for which postmarket general controls are not adequate to provide reasonable assurance of safety and effectiveness, but there is sufficient information to develop “special controls” to provide such assurance. Special controls may include performance standards, postmarket surveillance, patient registries, guidelines, recommendations, and other “appropriate” actions as determined by FDA.

- **Class III**—devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device, and the device is for use in supporting or sustaining human life or of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury. Class III devices require premarket approval in which safety and effectiveness are demonstrated in a premarket approval (PMA) application, typically including a substantial clinical trial, advisory panel review, and a manufacturing inspection.

The animating idea behind the statutory creation of three classes of devices is a risk-based approach, tailoring the type of premarket review (or exemption) to the riskiness of the device. A point often overlooked is that all three classes of devices (Class I, II, and III) reach the market on the same legal footing. A riskier device naturally receives more detailed premarket review. But its legal standing is no different than a less risky device that is exempt from premarket review altogether. In all cases, FDA must find that the totality of premarket review and postmarket controls provide reasonable assurance of safety and effectiveness.

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\(^1\) Federal Food, Drug, and Cosmetic Act (FDCA), as amended, § 513(a)(1).
\(^2\) See, *e.g.*, FDCA §§ 501, 502; 21 C.F.R. §§ 801, 803, 806, 807, 820.
When a firm wishes to market a medical device for the first time, or has significantly modified a device that is already marketed, the classification of the proposed device must be determined. By statutory default, \textsuperscript{3} the device is in Class III requiring PMA approval, unless FDA issues an order classifying it in Class I or II. To obtain such an order, the firm submits a premarket notification (or “510(k) submission”) demonstrating that the proposed device is substantially equivalent to a legally marketed Class I or II device or to a “preamendment” device marketed as of May 28, 1976. The comparison device is customarily called a \textit{predicate device}.

If FDA finds “substantial equivalence” (SE), then the proposed device is placed in the same class as the predicate device (\textit{e.g.}, Class I or II) and subjected to the same general and/or special controls to provide reasonable assurance of safety and effectiveness. If FDA finds the two devices are “not substantially equivalent” (NSE), then the proposed device remains in Class III and must receive PMA approval. There is a potential exception to this automatic Class III designation if the device is novel, but does not pose a level of risk that justifies Class III designation. In such cases, FDA has authority to develop a new (de novo) classification regulation classifying the device as Class I or II and specifying the controls needed to reasonably assure safety and effectiveness. \textsuperscript{4}

As FDA has observed:

510(k) review is both the mechanism by which a manufacturer seeks marketing authorization for a new device and by which FDA classifies devices into their appropriate regulatory category. Because devices are classified according to the level of regulatory control necessary to provide a reasonable assurance of safety and effectiveness, classification of a new device through the 510(k) process requires FDA to determine the issues of safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues. \textsuperscript{5}

A 510(k) filing may be unnecessary in some cases to determine classification. If a device falls within an existing classification regulation that has placed it in Class I (510(k)-exempt), the firm can proceed directly to market without contacting FDA. About two-thirds of the devices entering the market each year (67%) are

\textsuperscript{3} FDCA § 513(f)(1).
\textsuperscript{4} FDCA § 513(f)(2). To date, FDA has applied the “de novo process” to create classification regulations for 20 new devices.
\textsuperscript{5} Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] [Dec. 27, 2011] (hereinafter, “Draft Substantial Equivalence Guidance”) at 3. This draft guidance is well worth reviewing for a relatively complete and highly technical description of the substantial equivalence determination.

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510(k)-exempt. On the other side, if a device falls within a classification regulation placing it in Class III, then PMA approval is clearly required, and a 510(k) filing would be rejected. A miniscule 2% of devices enter the market each year via PMA approval or the humanitarian device exemption (HDE) variant. That leaves just under a third of new devices entering the market each year via 510(k) clearance.

This group comprises the “medium risk” category of primarily Class II devices. It is this cohort whose pace of development is controlled by FDA via the 510(k) process. These devices may be iteratively improved, but only within the bounds of substantial equivalence, or they risk being shunted to the PMA approval process. In most cases, the PMA process would not be commercially feasible, particularly if competing devices are still in Class II. Therefore, as a practical matter, an NSE decision (or pre-submission advice from FDA that an NSE decision is likely) will kill a proposed modification.

III. SUBSTANTIAL EQUIVALENCE DETERMINATION

The substantial equivalence determination is the heart of the 510(k) program. Under the statutory definition of this term, the proposed and predicate devices must have the same intended use. They may, however, vary in their technological characteristics, if the proposed device is shown to be equally safe and effective and does not present different questions of safety and effectiveness. Supporting data to show equivalent safety and effectiveness may include bench, animal, and/or clinical testing.

To understand substantial equivalence review, one should review the decision making flow chart FDA uses to implement the statute. There are potentially six decisions FDA needs to make:

Decision 1: Is the new device compared to a legally marketed predicate device? The first question FDA must answer is whether the 510(k) submission identifies at least one legally marketed device as the “predicate device.” Under FDA’s regulations, a legally marketed device may be: (i) a device legally marketed prior to May 28, 1976 (i.e.,

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7 Id.
8 A minority of Class I devices require 510(k) clearance. Some Class III devices still go to market via 510(k) clearance as FDA reviews whether they should be reclassified to Class I or II or calls for PMA applications.
9 FDCA § 513(i).
11 We will review the proposed version of the flow chart in the Draft Substantial Equivalence Guidance, Appendix A. The flowchart actually in use dates back to the K86-3 Guidance issued in 1986. The differences between them are not significant, at least not for purposes of this discussion.
a “preamendment device”) not subject to a final regulation placing the device type in Class III and calling for PMA applications; (ii) a device of a type that has been reclassified from Class III to Class II or Class I; or (iii) a device that has been specifically found SE to another Class I or II device through the 510(k) process.\(^\text{12}\)

A 510(k) submission must cite at least one such predicate device. However, in some cases, a submission will cite multiple predicates to exploit several prior clearances, each having a different indication for use and/or technological feature within the same device type and intended use.\(^\text{13}\) The use of multiple predicates allows a proposed device to combine technology previously offered only in separately cleared devices. However, the comparison to each predicate device must meet all elements of the statutory definition of substantial equivalence. FDA, in its discretion, also may allow citation to a previously cleared “reference device” that is not substantially equivalent to the proposed device, but supports evaluation of certain characteristics of a proposed device.\(^\text{14}\) But there would still need to be at least one predicate device meeting all requirements for substantial equivalence.

While any device cleared since 1976 theoretically may serve as a predicate, the usefulness of predicates tends to fade over time. Our office reviewed the first 100 consecutive clearances granted in 2013 and found that the median age of the predicate devices was 60.5 months (the average was 73.5 months; range 1 to 310 months).\(^\text{15}\) This slant toward more recent clearances makes sense; while it may be legally permissible to obtain clearance based upon ancient technology, it would generally be impractical from a business perspective to market such technology. On the other hand, if the proposed device has up-to-date technology but relies upon an ancient predicate, FDA would probably steer the submitter toward a more recent predicate, or require massive amounts of data to bridge the comparison to outdated technology. If a device type is relatively static (e.g., condoms), then older predicates may retain their value. But for a device type actively being improved, predicate devices generally have a shorter shelf life.

\(^\text{13}\) The “indications for use” describe the disease or condition the device will diagnose or treat, including a description of the intended patient population. Draft Substantial Equivalence Guidance at 13-14. The indications for use are a factor in determining intended use. \(\text{Id.}\)
\(^\text{14}\) \(\text{Id.}\) at 10-13.
\(^\text{15}\) We reviewed the first one hundred traditional 510(k) clearances, excluding Special 510(k)s, Abbreviated 510(k)s, and traditional 510(k)s when the 510(k) summary was not available online. Of the 100 clearances reviewed, 50 cited a single predicate and 50 cited multiple predicates; the total number of predicates cited was 200.
**Decision 2: Does the new device have the same intended use as the predicate device?** FDA’s determination of intended use of a device is based on the proposed labeling submitted in a 510(k).\(^{16}\) When a review of the indications for use and all other information in the proposed labeling submitted with a 510(k) supports an intended use that is the same as that of the predicate device, FDA will determine that the new device and predicate device have the same intended use. If the two devices do not have the same intended use, then the proposed device is precluded from the 510(k) pathway.

The determination of intended use is more elastic than might be supposed, and depends upon the level of generality at which a device’s intended function is defined. The point was recently illustrated in *Cytori Therapeutics v. FDA*.\(^{17}\) There, Cytori Therapeutics appealed an NSE determination for two devices capable of extracting stem cells from fat tissue. Cytori Therapeutics had compared these devices to predicate devices previously cleared for harvesting cells from blood and bone marrow. The company defined the intended use of both the proposed and predicate device as deriving cells and preparing cell concentrates from tissue. FDA, however, defined the intended use at a lower level of generality to include the tissue type. Thus, FDA’s position was that extracting cells from fat is a different intended use than extracting cells from blood, precluding a finding of substantial equivalence. The D.C. Court of Appeals deferred to FDA’s scientific expertise in choosing to distinguish cell extraction based upon tissue type, requiring only that the agency make a “reasonable decision reasonably explained.”\(^{18}\) With the bar set so low, the court easily found that FDA had met it.\(^{19}\)

**Decision 3: Does the new device have the same technological characteristics as the predicate device?** A 510(k) submission must identify the various features of the proposed and predicate devices, including design, materials, energy source, hardware/software, reagents, and so forth. Obviously, if the proposed and predicate devices are the same, then they will be found substantially equivalent.

**Decision 4: Do the differences in technological characteristics between the new device and the predicate raise different questions of safety and effectiveness?** If the proposed device raises different questions, then it will be found NSE. An example is provided in FDA’s recent draft guidance:

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\(^{16}\) FDCA § 513(i)(1)(E)(i).
\(^{17}\) *Cytori Therapeutics v. FDA*, No. 11-1268 (D.C. Cir., Mar. 22, 2013).
\(^{18}\) Id. at 9.
\(^{19}\) Id. at 9-10.
Predicate: A surgical ablation clamp ... used in open cardiac surgical procedures. The cardiac surgeon can clearly see the tissue on which energy is being delivered and can directly see the change in the tissue throughout the procedure.

New Device: A percutaneous cardiac ablation catheter that is used during a closed cardiac electrophysiology procedure, *i.e.*, a device that is inserted in a blood vessel and where the catheter tip is placed in the heart. The catheter is used by a cardiac electrophysiologist who relies on indirect visualization methods (*e.g.*, electrocardiography) to see the tissue he/she is ablating and the change in the tissue throughout the procedure. . . .

Intended Use: Same

Different questions of safety and effectiveness? Yes

Why: In this example, the specialist conducting the procedure with the new device is different from the predicate device. Moreover, the specialist using the new device relies on different visualization methods and endpoints, which involve different questions to determine the safety and effectiveness of the device. Because these types of questions were not necessary to take into account for the predicate device, the new device would be found NSE.*

*Cytori Therapeutics* provides another example. There, FDA pointed to the enzyme used to separate cells from fat tissue but not used in the predicate devices as posing “new safety questions based on its effect on harvested cells.”* Once again, the level of generality makes the formulation of questions flexible. FDA could have said that the proposed and predicate devices raise the same questions of safety, *i.e.*, the impact of harvesting methods on the cells. In that case, the company could have been asked to provide bridging data within the 510(k) process to show lack of impact from the enzyme versus the methods used to extract cells from blood. Instead, FDA defined the questions of safety at a lower level of generality, in terms of the specific technology used to extract the cells. Since the specific extraction technology is different for the two tissue types, FDA found the two devices NSE.

**Decision 5a: Are the methods for evaluating the different characteristics’ effects on safety and effectiveness acceptable?** If the questions of safety and effectiveness are the same between the proposed and predicate devices, FDA considers the scientific validity of the test methods used to show that the modified technological characteristics

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20 Draft Substantial Equivalence Guidance at 19.
21 *Cytori Therapeutics* at 5.
are safe and effective. One or more of the following test methods may be applicable depending upon the device:

- mechanical, electrical, and biological engineering performance testing;
- biocompatibility testing;
- electromagnetic compatibility (EMC) testing;
- sterility data;
- stability/shelf life data;
- software validation;
- laboratory testing;
- animal testing;
- cadaver testing; and
- clinical testing.

FDA has described its stepwise analytical consideration of the adequacy of the test methods in a 510(k) submission as follows:

First, FDA considers whether descriptive information about the technological characteristics, such as the materials, design, or specifications, of the new device is sufficient. Very few 510(k) submissions rely solely on descriptive information about materials, design, specifications, and other technological characteristics. . . . When this information is not sufficient to support a substantial equivalence determination, FDA then considers whether non-clinical performance testing data would be sufficient. Non-clinical performance testing includes a wide variety of test modalities that will be dependent upon the specifics of the actual device. Although FDA considers animal data as part of the non-clinical performance testing data, animal data are typically requested when other forms of non-clinical data are not sufficient to demonstrate substantial equivalence.

When non-clinical performance testing data are insufficient, or available scientific methods are not acceptable, e.g., the scientific methods are deemed unacceptable because they are not clinically validated or are not supported by a valid scientific rationale, FDA may request clinical performance data to support a substantial equivalence determination.23

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23 Id. at 20.
FDA currently reports requesting clinical data for fewer than ten percent of 510(k) submissions. As FDA has noted, “the clinical data necessary to support a 510(k) [may] involve a relatively small number of patients and . . . a simpler study design than is necessary to support a premarket approval (PMA) application. FDA considers any data involving human subjects to be clinical data.” FDA has supplied the following as an example of when clinical data may be required:

Some devices that display data about the patient’s anatomy or physiology, e.g., glucose meters, pulse oximeters, blood pressure cuffs, are supported by software. If there is a change in the software that relates to how the software analyzes the patient’s anatomy or physiology, the software may need to be tested on actual patients to assure that it performs in a manner that is equivalent to the previous version. In this case, non-clinical data may not suffice.

As another example, FDA provides the following:

The new device is an IVD [in vitro diagnostic] that is indicated for over-the-counter use, whereas the predicate device is indicated for prescription use in the home or prescription use in a clinical setting. Clinical data demonstrating that the user can collect the sample, generate an accurate result, and adequately interpret the result may be necessary to characterize whether the new device has equivalent safety and effectiveness as the predicate device. For some devices, however, this change may result in a new intended use and an NSE determination.

In most cases, there are scientific methods available to bridge the gap between the proposed and predicate device, whether bench, animal, or clinical. However, if such methods are not available, an NSE decision will issue.

**Decision 5b: Do the data demonstrate equivalence and support the indications?** At this last step, FDA may decline to find substantial equivalence if it concludes that the resulting safety and effectiveness data presented are insufficient to show that the proposed device is at least as safe and effective as the predicate device. In such cases, applicants may be advised as to specific additional information that could potentially lead to a finding of substantial equivalence. Thus, an applicant may provide significant additional data in response to an additional information (AI) request and/or submit multiple 510(k) notifications before obtaining clearance.

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24 Id.
25 Id. at 21.
26 Id. at 22.
27 Id.
In the early days of the 510(k) program, a submission could be quite short and consist merely of a narrative description of the proposed device versus the predicate device. Those days are long gone. It is not uncommon for applicants to undergo multiple iterations of responding to requests for information and acquiring significant additional bench, animal and/or clinical data at FDA’s direction (i.e., to respond to FDA’s questions) before clearance is granted. The process can last a few months to several years.

IV. STRENGTHS OF SUBSTANTIAL EQUIVALENCE REVIEW

After a proposed device and predicate device are found substantially equivalent, the newly cleared device itself becomes available as a baseline for future comparison, i.e., a predicate device. This chain of linked comparisons allows for controlled technological evolution. The evolutionary approach fits well with the iterative development of most Class I/II device technology. FDA effectively steers the technology from point to point, allowing advances only far enough that the likely clinical impact can be predicted. If a proposed device gets too far ahead, FDA designates it as a Class III device requiring PMA approval.

The 510(k) program has a number of strengths that have been little recognized. In this discussion below, we will review the most important advantages offered by substantial equivalence review.

A. Leveraging FDA’s Review Experience

A clearance obtained by each market participant is a potential building block for substantial equivalence available to all market participants. For example, suppose Firm X obtains clearance for Device A with Feature B, an incremental improvement over all competing technology. The predicate device is Device A without Feature B. Firm X provides significant bench and animal testing data to show that the addition of Feature B does not adversely affect the safety or effectiveness of Device A. Once FDA has reached this finding, it becomes available to a competing firm that wishes to introduce Device A’ with Feature B’. FDA may require data to bridge the difference between Feature B and Feature B’, but the 510(k) program enables both FDA and industry to avoid continually reinventing the Feature B wheel.

As another example, consider FDA’s illustration of when it may allow a reference device to be used to assist a submitter to reach an SE decision in the substantial equivalence decision flow chart:

A manufacturer submits a 510(k) for a total knee implant with coating X (the new device). Other coated knee implants with the same intended use with coatings A,
B, and C are legally marketed. In addition, a total hip implant with coating X is legally marketed. The manufacturer cites the legally marketed knee implant with coating A as the predicate device. FDA determines that the new device has an appropriate predicate device (thus, answering “yes” at Decision Point 1) and the new device has the same intended use as the predicate device (thus, answering “yes” at Decision Point 2 in the Flowchart). However, FDA determines that the new device does not have the same technological characteristics as the predicate device (thus, answering “no” at Decision Point 3 in the Flowchart), because the new device (knee implant with coating X) has a chemical profile different from the chemical profile of the cited predicate device (knee implant with coating A). There are no other technological differences between the new device and the cited predicate device (knee implant with coating A). FDA determines that the new device does not raise different questions of safety and effectiveness. In this case, FDA determines that the safety and effectiveness questions regarding the coating material are whether it is biocompatible and whether it impacts the fixation of the implant, and these questions apply to both the new device and predicate device (thus, answering “no” at Decision Point 4 in the Flowchart).

After Decision Point 4 in the Flowchart, if appropriate, the manufacturer may refer to the reference device (the hip implant with coating X in this situation) to support the appropriate scientific methods for the characterization of coating X on the new knee implant device. In this particular example, the manufacturer provided an adequate scientific rationale to support that the methods used to characterize the biocompatibility and characteristics of the coating (e.g., strength, abrasion, etc.) on the hip implant are applicable to the knee implant. The reference device (hip implant with coating X) is used in this case solely to assist with the characterization of the coating on the new device (knee implant with coating X).

In short, the open regulatory architecture of the 510(k) program enables FDA and industry to leverage the entire body of FDA’s review experience. Correspondingly, it enables specific sectors of the device industry to leapfrog through the regulatory process more rapidly than any one firm could on its own, each taking advantage of other firms’ clearances as they steadily improve the technology. The open regulatory architecture does not lessen the rigor of the scientific review, but rather, reduces its scope by allowing FDA’s prior scientific determinations to be incorporated. As discussed earlier, the reliance on prior scientific determinations occurs only when FDA explicitly concludes that they are relevant to the case at hand.

Draft Substantial Equivalence Guidance at 12-13 (footnotes omitted; emphasis supplied).
The PMA program, in contrast, has a closed regulatory architecture. Each applicant must prove their device from the ground up. FDA is forbidden from relying upon information from prior PMA approvals in the assessment, no matter how relevant or useful, unless the previous applicant grants the new applicant an express written authorization. A right of reference is not usually granted absent a monetary payment or licensing agreement of some kind. It is therefore not practical to leverage FDA’s previous scientific findings when reviewing similar technology. This closed regulatory architecture increases the burden of each PMA review on FDA and industry and slows the pace of innovation. In this regard, it is virtually the opposite of the 510(k) program.

B. Appropriate Focus on Modifications

A closely related aspect of the open regulatory architecture is that it allows FDA and industry to focus on modifications, i.e., the delta between a proposed device and a predicate device. It may make sense for truly novel intended uses or technology to conduct a ground up assessment (including a significant premarket clinical study), because the clinical performance of novel technology is likely to be difficult to predict. But for well characterized technology that has been incrementally improved, this type of premarket review is almost always a waste of resources. This is especially true if FDA has already made relevant scientific determinations that can be brought to bear.

The focus on the delta is scientifically possible because many Class I/II devices can be validly disaggregated as to elements of safety and effectiveness (e.g., biocompatibility, electrical safety, mechanical performance, and sterility). All elements can be analyzed using a combination of findings from FDA’s prior review of similar technology, conformance to FDA-recognized or other standards, and bench, animal, and/or clinical testing as needed. The combined data set provides a solid scientific basis for predicting the clinical performance of a proposed device.

29 21 C.F.R. § 814.20(c) (2010).
30 A little used statutory provision allows data in an existing approval to be used for other approvals after six years has elapsed. FDCA § 520(h)(4).
31 There are voluntary standards developed and maintained by various entities in the U.S. and around the world, many of which FDA has recognized. FDCA § 514(c). FDA allows 510(k) submitters to invoke standards to streamline 510(k) submissions and address information needs for substantial equivalence determinations. Guidance for Industry and FDA Staff, Use of Standards in Substantial Equivalence Determinations (Mar. 12, 2000). Further, FDA has created the Abbreviated 510(k), which allows a declaration of conformity to a recognized standard to expedite review of a 510(k) submission. In the first two months of 2013, according to my search of the 510(k) database, there were 471 clearances, of which 14 clearances were Abbreviated 510(k)s.
C. Regulatory Predictability

A device clearance is binding on FDA as an established baseline for comparison. The binding nature of a clearance is critical in providing a reasonable degree of regulatory predictability. A firm intent on introducing modified technology can survey past clearances and gain a good understanding of what aspects of the technology FDA has reviewed, what conclusions it has reached, what modifications will potentially raise regulatory concern (due to the absence of prior FDA review), and what testing will likely be required to address the concern. If FDA had authority to reject prior clearances at will, this predictability would be lost.

In this respect, the 510(k) program bears more than a passing resemblance to common law judging. Both systems rely on stare decisis to provide stable rules of decision, but utilize the flexibility of case-by-case adjudication to respond to new or varied circumstances. Like common law judges, FDA reviewers are constrained by prior decisions, but also have significant discretion to determine the applicability of prior decisions to the case at hand. As discussed above, the applicability of predicate device clearances to the review of a proposed device is heavily dependent upon how one characterizes the scope of the prior determination. Cytori Therapeutics illustrates that the agency is adept at distinguishing predicate devices when it wishes to do so. That case also shows that the standard of judicial review is so deferential that FDA is effectively the final decision maker in this regard.\(^\text{32}\)

In the common law, a precedent that is clearly erroneous can be overruled by the higher level courts. Although precedents are more often distinguished or forgotten than overruled, the ability to correct manifest error is an important part of any legal system. Legally, a device cannot serve as a predicate if it has been removed from the market at FDA’s initiative or determined to be misbranded or adulterated by judicial order.\(^\text{33}\) These events are rare. In a few cases, FDA has administratively rescinded (or obtained the owner’s “voluntary” consent to withdrawal) of 510(k) clearances based upon a gross safety issue or fraud in the inducement.

From a practical perspective, FDA reviewers routinely find ways to require 510(k) submitters to address problems that have surfaced from postmarket clinical experience with predicate devices. Additionally, if evidence emerges that an entire Class II device type is systemically riskier than had been supposed, FDA has the authority to reclassify it to Class III, thereby retrospectively requiring all 510(k) holders to submit their marketed

\(^{\text{32}}\) See also Ivy Sports Medicine v. Sebelius, No. 11-1006, slip op. at 27-33 (D.D.C., Apr. 10, 2013) (deferring to FDA’s scientific comparison of proposed and predicate devices).

\(^{\text{33}}\) FDCA § 513(i)(2).
devices to the PMA approval process. This type of reclassification based upon new information is expressly contemplated in the statutory scheme.

Recently, FDA wrote to a trade association announcing that it will designate devices in the 510(k) database that have been recalled due to a serious design flaw.³⁴ Manufacturers who rely on these clearances as predicate devices must show that the issue has been addressed or that they rely on an aspect of the predicate device unrelated to the design flaw. Otherwise, the clearance letter (and database designation for the new device) will specify that the new device is substantially equivalent to a device recalled for a serious design flaw and, therefore, may itself be adulterated or misbranded.

One could plausibly argue for the adoption of a more formal mechanism for rescission of predicates in limited circumstances. My own view is that the need for this reform has not been shown, and that FDA has sufficient authority to correct errors or respond to manifest postmarket problems by the means just discussed.

D. Self-Sustaining Management of Device Heterogeneity

The case-by-case nature of 510(k) substantial equivalence review is well adapted to the heterogeneity of devices.³⁵ In a substantial equivalence review, a predicate device provides an established baseline against which to review the proposed device for equivalent safety and effectiveness. The submitter has an incentive to choose the baseline that most closely resembles the proposed device, and therefore, is most likely to be relevant to the review. This system easily accommodates a broad spectrum of devices types, including variations and subtypes, because the body of potential baseline technology consists of all the various devices that have been cleared. Indeed, the richness and heterogeneity of the available baseline technology is improved with each clearance.

Case-by-case adjudication of 510(k) submissions also has the distinct benefit of automatically incorporating the latest technology, preventing obsolescence of the baseline. It is similar to the body of common law decisions in which more recent decisions extend prior rulings to the latest social or technological developments, and older decisions fall into disuse as their social and technological premises become increasingly obsolete. The 510(k) program is thus self-sustaining in its management of the heterogeneity of devices and their constant technological advances.

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³⁴ This letter does not appear to be posted on FDA’s web site. I can supply a copy.
³⁵ See Appendix A to get a sense of the range of devices that FDA reviews.
V. HISTORICAL DEVELOPMENT OF THE 510(K) PROGRAM

Where did the 510(k) program come from? In 1976, Congress amended the Federal Food, Drug, and Cosmetic Act (FDCA) by adding the Medical Device Amendments (MDA), a complex new scheme for premarket and postmarket regulation of medical devices.\(^{36}\) Although Congress included a 510(k) procedure, it was expected to play a minor and transitory role. No one envisioned the system of substantial equivalence review that eventually developed.

The unplanned nature of the 510(k) program has been a source of criticism over the years.\(^{37}\) The critics’ tone has been one of reproach to FDA for failing to properly implement the statutory scheme, or regret that necessity required FDA to adopt the “shortcut” or “loophole” of substantial equivalence for most devices. To be fair to FDA, however, the original MDA was unworkable from the outset -- very little of it survived contact with reality. Large swaths of the MDA quickly became dead letters. Unless one posits a lazy or incompetent (or perhaps malevolent?) bureaucracy sabotaging an otherwise realistic statutory scheme over a long period of time, it is a fair inference that the fault lies with Congress not FDA.

Originally, the MDA decreed that FDA would review all existing types of medical devices and by regulation place them in Class I, II or III.\(^{38}\) Class I devices would be subject to various general postmarket controls (e.g., establishment registration, device listing, good manufacturing practice, or GMP). Class II devices would be subject to FDA-established performance standards and general postmarket controls.\(^{39}\) Class III would need premarket application (PMA) approval or a completed product development protocol (PDP) and would adhere to general postmarket controls.\(^{40}\)

After the existing device types were classified, all new device types developed after 1976 were to be placed in Class III, unless FDA could be persuaded to reclassify them to Class I or II. Flexible reclassification of device types would occur as new information emerged with experience.\(^{41}\) FDA was granted broad authority to issue

\(^{38}\) 90 Stat. 540-41.
\(^{39}\) 90 Stat. 546-552.
\(^{40}\) 90 Stat. 553-59.
\(^{41}\) 90 Stat. 544-45, 547, 553, 572.
regulations restricting the sale, distribution and use of specific devices as needed. FDA also could ban unsafe devices and/or require mandatory recalls and repair, refund, and notification remedies when needed.

Almost nothing went according to plan. The mere classification of existing device types took 14 years to complete, far longer than envisioned. FDA struggled to develop performance standards, which had been conceived as the centerpiece of regulatory control over Class II devices (only a handful have ever been issued). The distinction between Class I and Class II devices never took off. All of the device types placed in Class III were supposed to be subject to a prompt call for PMAs, but that process went so slowly that even today (i.e., 37 years later) it is not complete. Thus, for many years, “preamendment” Class III devices have reached the market via 510(k) clearance rather than PMA review, and that is still true for about two dozen of them.

Numerous other provisions failed to function as intended. The PDP option, intended to be on par with PMA approval, was a complete flop. An elaborate procedural regulation for banning devices was issued, but the authority was invoked once in 1983, and never again. Only a handful of mandatory recall orders have ever been issued; the refund authority was never used. FDA has only issued two restricted device regulations – one for hearing aids and the other for analyte specific reagents. The various reclassification procedures proved too burdensome and slow, and so have been rarely used. Elaborate procedures conferring administrative or judicial review of FDA decisions became cob-webbed from disuse.

From the statutory rubble, a portion of the MDA unexpectedly emerged as the dominant pathway to market. The MDA provided that if a new device were substantially equivalent to a preamendment device, it could proceed to market with the same classification and controls (or, if the device type were not yet classified, it would proceed to market subject to whatever classification and controls were later applied).

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42 90 Stat. 567.
44 This use of the 510(k) process for Class III devices has been subject to legitimate criticism. It is irrelevant, however, to an evaluation of the 510(k) process as applied to Class II devices.
46 An elaborate procedural regulation for this rarely used procedure was issued in 1996 (21 C.F.R. Part 810).
48 A recent statutory reform attempts to make this process less burdensome. See The Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, § 608(a) (2012) (modifying section 513(e) of the FDCA).
The concern was that those already in the market in 1976 not gain a competitive advantage during the transition to the final regulatory scheme envisioned in the MDA.

This pathway to market was called “510(k) clearance” or “premarket notification” after section 510(k), which the MDA had added to the FDCA. Section 510(k) required that a firm intending to bring a new device to market via substantial equivalence notify FDA 90 days in advance. By 1984, however, a noted commentator could write that 510(k) provisions had “in many ways eclipsed detailed statutory [PMA] provisions so painstakingly drafted” as the route to market for most medical devices.49

The key to 510(k) clearance was the concept of substantial equivalence. Although the MDA had used the term, it did not provide a definition. It took FDA a decade (to 1986) to publish a working definition.50 Furthermore, the MDA did not spell out most elements of a workable 510(k) program, because it had conceived of the 510(k) process as a transitional measure. The watershed event for substantial equivalence review from a statutory perspective was the Safe Medical Devices Act of 1990 (SMDA).51 The SMDA ratified the FDA’s 510(k) program and placed it on a sound statutory footing.52

First, the SMDA codified the definition of substantial equivalence that FDA had developed administratively through the experience of applying the concept for 14 years. The definition was designed as a screen to ensure that the predicate device would be sufficiently relevant to the proposed device to be a valid comparator and to require that the proposed device be at least equally safe and effective as the predicate device. The SMDA also confirmed FDA’s power to require clinical data in the 510(k) context.

Second, the SMDA ended the legal necessity to cite a pre-MDA predicate device, so that devices cleared after enactment of the MDA could be used as predicates without constructing a clearance chain back to a pre-MDA predicate device. This freed the comparative process from 1976 technology and allowed the state of the art to evolve more freely.

Third, although the SMDA did not completely throw in the towel on regulating Class II devices by FDA-developed performance standards, it made them optional for FDA. It did so by introducing the concept of discretionary “special controls” for Class II

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devices, which permitted a variety of measures in FDA’s discretion, including but not limited to, performance standards and guidelines for requiring a 510(k) submission with clinical data. However, the only special control FDA uses with any regularity is issuance of guidance documents for the content of 510(k) submissions.53

In 1996, FDA successfully reformed the 510(k) program in a number of ways, streamlining the process and reducing a vexing backlog of 510(k) submissions that had developed.54 These reforms were augmented by statutory improvements enacted in the Food and Drug Administration Modernization Act of 1997 (FDAMA).55 In the 2009-2012 time frame, FDA once again undertook a process of administratively reforming the 510(k) program.56 Thus, the 510(k) has never been considered beyond reproach. It has evolved over time, and has been repeatedly refined according to the dictates of experience.

If there is a pattern to the failures of the original MDA, it was over-confidence in the capabilities of centralized agency regulation. Congress seems to have imagined that FDA would orchestrate the device industry from Washington D.C. with a degree of mastery and subtlety that proved impossible. In particular, the idea that performance standards would be the primary method for regulating Class II devices was an utter failure. The establishment of a viable PMA process for many Class III devices was more successful, but it took decades to complete most of it, and some Class III devices still utilize the 510(k) pathway. It also was impractical to have supposed, as Congress apparently did in 1976, that the resource intensive PMA process could be widely applied. Fortunately, FDA developed the 510(k) program from an ill-defined transitional measure to a robust pathway to market, and a later Congress had the good sense to ratify it in the SMDA. If FDA had not done so, the inventive and vibrant device industry we have today might have been strangled in the crib.

53 On March 9, 2013, I searched FDA’s device guidance database for “Class II Special Controls Guidance Document” and 481 documents were returned, including both final and draft guidance. E.g., Guidance for Industry and FDA Staff – Class II Special Controls Guidance Document: Full Field Digital Mammography System (Mar. 27, 2012).


56 510(k) Working Group Preliminary Report and Recommendations (Aug. 2010); Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations (Aug. 2010); Institute of Medicine, Medical Devices and the Public’s Health: The FDA 510(k) Clearance Process at 35 Years (2011); CDRH, Plan Of Action For Implementation of 510(K) and Science Recommendations.
VI. THE INSTITUTE OF MEDICINE’S CALL TO SCRAP THE 510(K) PROCESS

Perhaps the most spectacular rejection of the 510(k) process appears in the Institute of Medicine’s Medical Devices and the Public’s Health: The FDA 510(k) Clearance Process at 35 Years (2011) (IOM Report). The IOM Report presents a learned and worthwhile summary of the origins, history, and operations of the 510(k) program. After considering all of this information, the IOM report concludes that the 510(k) program should be scrapped.

When one unpacks the basis for the IOM committee’s drastic recommendation, it oddly appears not to be based upon a pragmatic assessment of the fruits of the 510(k) process, as one might have expected. Rather, it relies upon a misplaced theoretical concern underpinned by a flawed legal analysis.

FDA asked the IOM committee to evaluate the 510(k) program and make recommendations for improvement. The first signs of trouble appear in the Preface, which expresses the committee’s angst about its assignment:

In reviewing the legislative and regulatory history of the 510(k) program, the committee found that it was designed in 1976 to provide only a determination of the substantial equivalence of a new device to an already marketed (predicate) device; it was not designed to determine whether a new device provides a reasonable assurance of safety and effectiveness or whether it promotes innovation. That finding complicated the committee’s work in that the FDA, in the charge to the committee, stated that the goals of the 510(k) clearance process are to “make available to consumers devices that are safe and effective” and to “promote innovation in the medical device industry.” The committee struggled with how to address the conflict between the legislative framework of the program and the FDA’s stated goals.57

The fatal flaw in the IOM committee’s finding is that the statutory design of the 510(k) program in 1976 was superseded in 1990 by the SMDA. Under the latter, a device cleared via the 510(k) program is one for which FDA has found that a Class I or Class II designation (and associated controls) provides a reasonable assurance of safety and effectiveness. Yet, throughout the report, the committee repeatedly ignores the legal implications of the SMDA and cites the 1976 statutory framework to evaluate the legal standing of the current 510(k) program.58 The committee’s citation59 to Medtronic

57 IOM Report at xi-xii.
58 See, e.g., id. at 36-37.
59 IOM Report at 36.
v. Lohr\textsuperscript{60} for validation of its legal analysis is particularly telling, because that case involved a product cleared under the statutory framework in place prior to the SMDA.\textsuperscript{61}

At bottom, the IOM’s committee concern appears to be that today’s devices trace back to an original predicate that never received a complete PMA-style evaluation of safety and effectiveness, including a clinical trial. In Finding 2-1, the IOM report states: “The safety and effectiveness of individual 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.”\textsuperscript{62}

The grudging concession in the second sentence of Finding 2-1 points to the reason the committee’s concern is not really one to worry about (much less justify scrapping the 510(k) program altogether). The purpose of premarket review is to predict or characterize in advance the likely clinical performance of a device, in order to avoid unexpected adverse consequences. Now that 37 years have passed, the cohort of Class II devices have a long history of clinical use. They are generally well characterized as to their expected behavior. Further, their technology has been improved substantially over the years as would be expected. And regulations requiring reporting to FDA of adverse events, malfunctions and recalls have been in place for decades. This clinical and regulatory experience (and technological improvements) negates the concern that ancient versions of these devices did not undergo a clinical trial.\textsuperscript{63} If there were in fact a public-health crisis related to unsafe or ineffective Class II medical devices, FDA and/or device users would know about it. The committee wisely denies that it believes such a crisis exists.\textsuperscript{64}

**VII. IMPROVEMENT NEEDED IN 510(K) TRANSPARENCY**

A persistent industry criticism of FDA’s implementation of 510(k) review is of its excessive unpredictability, particularly as to what testing data will be required to show substantial equivalence. A likely root cause of this problem is insufficient transparency in 510(k) decisions. Specifically, for the 510(k) program to operate predictably, industry must have access to the essential information in prior 510(k) decisions, such as the intended use and technological characteristics of the proposed and predicate devices, and the data provided to show substantial equivalence. This information is needed to

\textsuperscript{60} Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996).
\textsuperscript{61} See, e.g., Hall at 742.
\textsuperscript{62} IOM Report at 32.
\textsuperscript{64} IOM Report at 6.
allow a sponsor seeking clearance of a proposed device to hunt for predicate devices, learn FDA’s existing data requirements, and/or extrapolate likely additional data requirements that might apply to a proposed device that modifies existing technology.

A fact of 510(k) review is that FDA’s data and labeling requirements evolve iteratively, as experience is gained in the clinical use of particular device technology and to address the risks and challenges posed by continuing modifications. This process is the regulatory doppelgänger to the iterative development of the underlying device technology. Unfortunately, the evolution of regulatory requirements often is not well publicized, and so 510(k) applicants are often surprised by “new requirements” that seem to come out of nowhere. In fact, these FDA requirements are often rational responses to new knowledge and experience, or to technological modification, but the process is not sufficiently transparent to allow prospective applicants to know about or extrapolate new or additional requirements.

The chief culprit is likely the lack of easily searchable information describing the basis for FDA’s 510(k) decisions. The public 510(k) database is clunky and difficult to search. There are also summaries of the 510(k) decisions prepared by the submitter, which are supposed to provide information about the proposed and predicate devices, and the supporting data and conclusions to be drawn from it.65

In general, however, even reasonably forthcoming versions of these summaries are inadequate to provide a clear picture of the 510(k) decision, and many are deliberately vague. Worse, the submitter may opt out of providing a summary, based upon a commitment to provide a full copy of the 510(k) upon request within 30 days.66 This makes detailed information about the clearance virtually impossible to obtain in an electronic search, and FDA frankly does not provide meaningful enforcement if the submitter fails to supply a copy of the 510(k) within the required time, or at all.

In short, the public is operating from a degraded database as compared to FDA reviewers, who have access to complete 510(k) files, the decision memoranda, and institutional knowledge of their prior decisions. The current lack of ready access to important decision data creates a cloudy picture of prior clearance decisions and that is a large part of the reason that industry finds FDA’s 510(k) decisions unpredictable.

This issue may seem like small potatoes. But try this thought experiment. Suppose all judges have access to a complete full text searchable database of published decisions, can easily find and review relevant precedents and take them into account

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while deciding new cases and writing their opinions. At the same time, suppose litigants and their counsel only have access to a different database with case squibs, not entire decisions; that the database is partially indexed; and that it is not full text searchable. Suppose that a percentage of decisions are omitted entirely at the option of the litigants in the case, although if known to the searcher or found via the partial index, these litigants can be asked to mail the requestor a copy in 30 days (but there is no penalty if they do not comply). Suppose any complete decision can be obtained upon request (and payment of costs) to the court, but in an uncertain time frame that can range from four to 18 months.

Would this situation not make legal research substantially more difficult? Would it not make judicial decisions wildly more difficult to predict? Yet, this hypothetical fairly accurately describes the problem facing device companies and their regulatory consultants and counsel today. This paucity of information would be considered intolerable in the judicial system, and likewise it is intolerable in the 510(k) program. Both systems are precedent-driven, which requires access to the decision and reasoning in prior cases.

An important step toward greater transparency is readily available. Since 2004, without much fanfare, the office at FDA that reviews in vitro diagnostic (IVD) technology (now called the Office of In Vitro Diagnostics and Radiological Health, or OIR) has been publishing “decision memoranda” on which their 510(k) clearances are based. The memoranda generally describe the proposed and predicate devices, the data submitted, and the substantial equivalence reasoning. Many more devices, however, are reviewed by the Office of Device Evaluation (ODE), which does not publish the decision memoranda.

Presumably, ODE reviewers already prepare some kind of memoranda to justify clearance decisions. The simple posting of these memoranda in the 510(k) database should not be a significant expense or burden. It would not be necessary to undertake a grand project to impose a standard format on decision memoranda. A standardized format could actually be harmful in eliminating the nuance and detail that pervades so much of substantial equivalence decision-making in the heterogeneous world of devices. The decision memoranda simply need to document (as they already likely do or certainly should do) the key elements of the substantial equivalence decision (description of the proposed and predicate devices, the data submitted, and the substantial equivalence reasoning). In the longer term, the 510(k) database (with decision memoranda added) should be converted to easy full text searching. With so much of the treatment of proposed devices hinging on FDA’s prior clearance decisions, it is important for FDA to provide as much transparency as possible regarding these decisions.
When preparing some 510(k) submissions, it would be helpful to have access to the entire submission and relevant correspondence with FDA. For example, during the review process, FDA often issues at least one “additional information” letter describing deficiencies in the submitted information. This correspondence itself is a valuable window into requirements that may apply. Right now, an FOIA (Freedom of Information Act) request for a 510(k) file has an entirely unpredictable timeline for fulfillment. It can be anywhere from a few months to a couple of years. FDA should modify its FOIA program to provide a short, predictable timeline for the disclosure of 510(k) files.

Ultimately, there should be an up-to-date and publicly searchable 510(k) database consisting of all 510(k) files in full text searchable format (including the original submission, relevant correspondence, clearance letter, cleared indications for use, and FDA’s decision memorandum). Of course, there are obstacles to be overcome. For instance, all files must be redacted for trade secret and commercial confidential information. Another example is that NSE letters are not disclosable but may contain important AI requests that ideally would be included in the database. However, it is not beyond the capacity of industry and FDA to jointly solve these problems. This more complete transparency would greatly improve the predictability of the 510(k) process, and also would reduce the costs associated with finding predicate devices.

VIII. FUTURE OF THE 510(K) PROGRAM

The substantial equivalence approach to premarket review of medium risk medical devices has stood the test of time. As demonstrated above, the comparison to predicate device technology allows FDA to review of the safety and effectiveness of proposed devices based upon sound science and valid regulatory reasoning. Further, substantial equivalence review resembles the common law in providing a regulatory framework that is predictable, can handle device heterogeneity and technological advances, and is self-sustaining. As a practical matter, the 510(k) program has fostered increasingly beneficial and safe medical device technology, demonstrating that it is worth preserving.

For these reasons, I predict the 510(k) system will remain in place for the foreseeable future. It is not perfect, and continued statutory and administrative reform is inevitable – including, hopefully, the proposed transparency reform just discussed. Over the next few decades, we will likely need to significantly expand the Class II cohort beyond those device types that existed in 1976. I would therefore recommend reform of the de novo process so that more novel but medium risk device types can be readily placed in Class II. The process is currently too difficult, as suggested by the fact that only 20 device types have been classified in this way since 1997.
Also, the purported statutory distinction between Class I and Class II does not exist in reality. It is fine to maintain the option for special controls for Class II devices, but the only thing that really distinguishes Class I and II in practice is the 510(k) requirement. It would be better to acknowledge reality and make all Class I devices 510(k) exempt and all Class II devices subject to 510(k) review (moving the minority of Class I devices requiring 510(k) clearance to Class II and moving the minority of Class II devices exempt from 510(k) clearance to Class I).

Finally, it is amazing that the 510(k) program evolved from a transitional measure in 1976 to a robust pathway to market. Still, it is not unusual for complex statutory schemes to evolve, often with an interplay between statutory directives and bureaucratic implementation. In this paper, therefore, I have tried to describe substantial equivalence review as it operates today rather than as envisioned almost 40 years ago. As I have tried to convey, the 510(k) program we have today is quite sound and well worth the effort of reforming for the future.

Jeffrey K. Shapiro, HLS ’86
Director, Hyman, Phelps & McNamara
Washington, D.C.
jshapiro@hpm.com

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