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Substantial Equivalence Premarket Review: the Right Approach for Most Medical Devices

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I. INTRODUCTION

The Food and Drug Administration's (FDA) 510(k) program is the dominant pathway to market among medical devices. Of devices requiring premarket review, about 2% reach the market via premarket application (PMA) approval or the Humanitarian Device Exemption (HDE) variant, while the remaining 98% receive 510(k) clearance.¹

A 510(k) clearance is based upon a finding of "substantial equivalence" (SE). To make this finding, FDA compares a new device to one or more "predicate devices" previously 510(k)-cleared for the same intended use to determine whether, despite differences in technological characteristics, the new device is at least as safe and effective and does not raise different questions of safety or effectiveness. If the answer is yes, then the new device is cleared to market. This comparative review has proven well-suited to the broad range of moderate risk devices.

Nonetheless, substantial equivalence review is much criticized. It is frequently compared unfavorably to PMA approval as a means of establishing the safety and effectiveness of new devices,² as an affront to the original intent of the Medical Device Amendments of 1976 (MDA),³ and as a "regulatory loophole" that should be scrapped or, if that is not practical, at least limited to the extent possible.⁴ A much-publicized empirical study purports to show that devices receiving 510(k) clearance are responsible for a disproportionate share of the most serious recalls as compared to devices receiving PMA approval.⁵ The popular press often explains 510(k) clearance to the public as

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¹ Institute of Medicine (IOM), *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, at 4 (2011) [hereinafter "IOM Report"]. In fiscal year 2013, FDA issued 2,895 clearances and 44 PMA approvals. FDA, Agenda for Quarterly Meeting on MDUFA III (FY 2013-2017) Performance, at 6, 157 (Apr. 29, 2014). These numbers are typical of the annual gap between 510(k) clearances and PMA approvals.

² B. Goldberger, *The Evolution of Substantial Equivalence in FDA's Premarket Review of Medical Devices*, 56 *FOOD & DRUG L.J.* 317, 318, 330 (2001); M. Van Buren, *Closing the Loopholes in the Regulation of Medical Devices: The Need for Congress to Reevaluate Medical Device Regulation*, 17 *HEALTH MATRIX* 441, 460 (2007).

³ Pub. L. No. 94-295, 90 Stat. 539 (1976).

⁴ B. Goldberger, *supra* note 2, at 335-36; M. Van Buren, *supra* note 2, at 449-50, 460-461; J. Bauman, *The "Déjà vu Effect," Evaluation of United States Medical Device Legislation, Regulation, and the Food and Drug Administration's Contentious 510(k) Program*, 67 *FOOD & DRUG L.J.* 337, 360-61 (2012).

⁵ D. Zuckerman, et al., *Medical Devices Recalls and the FDA Approval Process*, 171(11) *ARCH INTERN MED.* 1006-1011 (2011); Alicia Mundy & Jon Kamp, *Device Review Process Faulted: Most Recalled Medical Products Were Cleared in an Abbreviated Manner, Study Says*, *WALL STREET J.*, Feb. 15, 2011.

“streamlined” or “abbreviated,” as if PMA approval were the norm.⁶ Perhaps most spectacularly, FDA requested that the prestigious IOM review the 510(k) process and recommend improvements.⁷ The IOM responded with a report concluding that substantial equivalence review cannot ensure safe and effective medical devices and should be scrapped.⁸

All of this criticism should be rejected. To demonstrate that substantial equivalence is the right approach for most medical devices requiring premarket review, this article will examine substantial equivalence review in detail. Section II recounts its historical development. Section III describes the legal framework in which substantial equivalence review operates. Section IV looks at the structure of FDA’s substantial equivalence decision-making, i.e., the specific decision steps FDA follows to reach a substantial equivalence determination. Section V describes how substantial equivalence review fosters a system that is efficient, predictable, and adaptable. This section establishes that substantial equivalence review is a powerful regulatory tool allowing FDA to ensure that the broad range of moderate risk devices meet the statutory requirement of reasonable assurance of safety and effectiveness. Section VI rebuts prominent criticism of substantial equivalence review. Section VII argues that a better public 510(k) database would improve the predictability of substantial equivalence review. Section VIII concludes by suggesting that substantial equivalence review is a sound approach for most medical devices and that criticism of it should be directed toward sensible reform rather than blanket condemnation.⁹

II. A STATUTE GOES AWRY

In 1976, Congress amended the Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA) by adding the MDA, a complex scheme for premarket and postmarket regulation of medical devices.¹⁰ Although Congress included a 510(k) substantial equivalence procedure, it was expected to play a minor and transitory role. No one envisioned the 510(k) pathway to market that developed.

This unexpected result has been a source of criticism over the years.¹¹ The critics’ tone has been one of reproach to FDA for failing to properly implement the statutory scheme. To be fair to FDA, however, the original MDA turned out to be unworkable – 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 the statutory scheme over decades, it is fair to conclude that the fault lies with Congress, not FDA.

The MDA decreed that FDA would review all existing types of medical devices and by regulation place them in Class I, II, or III.¹² Class I devices would be subject to general postmarket controls (e.g., establishment registration, device listing, good manufacturing

⁶ E.g., Alicia Mundy, *Firms Warn of Delays from FDA Scrutiny*, WALL STREET J., Sept. 30, 2009.

⁷ Established in 1970, the IOM “is an independent, nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public.” The IOM seeks to improve the nation’s health and conducts studies mandated from Congress, federal agencies, and independent organizations, in furtherance of that goal. About the IOM, <http://www.iom.edu/About-IOM.aspx> (last visited July 12, 2014).

⁸ IOM Report at 5-6.

⁹ This article does not discuss whether and to what degree 510(k) clearance should have preemptive effect in state law products liability lawsuits, although some of the discussion may be relevant to that question.

¹⁰ Medical Device Amendments of 1976, *supra* note 3.

¹¹ See, e.g., Goldberger, *supra* note 2; Bauman, *supra* note 4; M. Van Buren, *supra* note 2.

¹² 90 Stat. at 540-41.

practice). Class II devices would be subject to FDA-established performance standards plus general postmarket controls.¹³ Class III would be subject to PMA approval or a completed product development protocol (PDP), plus general postmarket controls.¹⁴

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 into Class I or Class II. Flexible reclassification of device types would occur as new information emerged with experience.¹⁵ FDA was granted broad authority to issue regulations restricting the sale, distribution, and use of specific device types as needed.¹⁶ FDA also could ban unsafe devices and/or order mandatory recalls and repair, refund, and notification remedies.¹⁷ In short, the congressional vision was to provide FDA with ample authority to conduct risk-based regulation of devices from cradle to grave.

Almost nothing went according to plan. The mere classification of existing device types took 14 years to complete, far longer than anticipated. FDA struggled to develop performance standards, which had been conceived as the centerpiece of regulatory control over Class II devices. Although a regulation was promulgated in 1980 with a procedure for developing standards,¹⁸ few have ever been issued.¹⁹ All of the device types on the market when the MDA was enacted were automatically placed in Class III and were expected to be promptly reviewed for retention in Class III (with a prompt call for PMAs) or down classified to Class I or II. Because the process went so slowly, this expectation was reiterated and reinforced by Congress in the Safe Medical Devices Act of 1990 (SMDA).²⁰ Nonetheless, even today, the process is not complete. As a result, for many years, so-called preamendment Class III devices have reached the market via the 510(k) pathway rather than PMA approval, and that is still true for about two dozen device types, such as semi-constrained artificial metal-on-metal hip joints, intra-aortic balloon and control systems, sorbent hemoperfusion systems, and external pacemaker pulse generators.²¹

¹³ *Id.* at 546-552.

¹⁴ *Id.* at 553-59.

¹⁵ *Id.* at 544-45, 547, 553, 572.

¹⁶ *Id.* at 567.

¹⁷ *Id.* at 560, 562-63.

¹⁸ 21 C.F.R. Part 861.

¹⁹ *E.g., id.* Part 1000.

²⁰ Pub. L. No. 101-629, § 4, 104 Stat. 4511, 4515-17 (1990) (setting a 1996 deadline for promulgating regulations calling for PMA applications for devices retained in Class III).

²¹ Government Accountability Office (GAO) Report 09-190, *MEDICAL DEVICES: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process* (Jan. 2009) [hereinafter "GAO Report"]. Since the GAO Report, FDA has steadily issued proposed and final rules to retain these remaining Preamendment Class III devices in Class III or downclassify them. *E.g.*, Effective Date of Requirement for Premarket Approval for Two Class III Preamendments Devices, 78 Fed. Reg. 4097 (Jan. 18, 2013); Cardiovascular Devices; Reclassification of Intra-Aortic Balloon and Control Systems for Acute Coronary Syndrome, Cardiac and Non-Cardiac Surgery, or Complications of Heart Failure; Effective Date of Requirement for Premarket Approval for Intra-Aortic Balloon and Control Systems for Septic Shock or Pulsatile Flow Generation, 78 Fed. Reg. 79,300 (Dec. 30, 2013); Effective Date of Requirement for Premarket Approval for Transilluminator for Breast Evaluation and Sorbent Hemoperfusion System (SHS) Devices for the Treatment of Hepatic Coma and Metabolic Disturbances; Reclassification of SHS Devices for the Treatment of Poisoning and Drug Overdose, 79 Fed. Reg. 3088 (Jan. 17, 2014); Effective Date of Requirement for Premarket Approval for an Implantable Pacemaker Pulse Generator; 77 Fed. Reg. 37,573 (June 22, 2012). A statutory amendment in 2012 gave FDA the authority to alter device classification by administrative order rather than regulation, which should speed the process. Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, § 608, 126 Stat. 993, 1055 (2012). The use of the 510(k) process for Class III devices is a transitional problem that is not relevant to an evaluation of the 510(k) process as applied to Class I and Class II devices. *See, infra*, note 66, and accompanying text.

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 for prosthetic hair fibers, and never again.²² Only a handful of mandatory recall orders have ever been issued;²³ the refund authority was never used.²⁴ FDA has only issued two restricted device regulations – one for hearing aids, and the other for analyte specific reagents.²⁵ The various reclassification procedures proved burdensome and slow, and so were used rarely.²⁶ Elaborate procedures conferring formal administrative review of FDA decisions became cob-webbed from disuse.²⁷ To this day, the dominant procedure for appeal is an informal supervisory review process set forth in a short regulation.²⁸

From the statutory rubble, a portion of the MDA unexpectedly emerged as the dominant pathway to market for medical devices. 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). The concern was that those devices already in the market in 1976 did not gain a competitive advantage during the transition to the final regulatory scheme envisioned in the MDA.²⁹

This pathway to market was called “510(k) clearance” or “premarket notification” after section 510(k), which the MDA had added to the FFDCAs. Section 510(k) required that a firm intending to bring a new device to market via substantial equivalence simply notify FDA 90 days in advance. By 1984, a commentator could write that

²² 21 C.F.R. Part 895; *id.* § 895.101.

²³ An elaborate procedural regulation for this rarely-used procedure was issued in 1996. *Id.* Part 810. Almost all recalls are initiated by firms marketing medical devices pursuant to voluntary guidelines in *id.* Part 7.

²⁴ FFDCAs § 518(b)(2)(C). FDA has occasionally obtained equitable restitution by judicial order. *E.g.*, *United States v. Universal Mgmt. Servs., Inc.*, 191 F.3d 750, 760–62 (6th Cir. 1999).

²⁵ 21 C.F.R. § 801.421; *id.* § 809.30. The attempt to classify cigarettes as restricted devices did not survive judicial scrutiny. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000). FDA declares every PMA-approved device to be a restricted device under FFDCAs § 515(d)(1)(B)(ii), a move of questionable legality, although it has never been challenged.

²⁶ The MDA amended the FFDCAs in 1976 to authorize five different bases for reclassification: sections 513(e), 513(f), 514(b), 515(b), and 520(l). 126 Stat. at 1055-56.

²⁷ *E.g.*, 21 C.F.R. Part 16.

²⁸ *Id.* § 10.75. Congress has twice legislated to improve this regulation. In the Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105, § 120, 111 Stat. 2296, 2318-20 (1997), Congress required FDA to add a procedure for advisory panel review of scientific disputes. Administrative Practices and Procedures; Internal Review of Decisions, 63 Fed. Reg. 63,978, 63,982 (Nov. 18, 1998). In section 607 of FDASIA, Congress added section 571A to the FFDCAs, which requires FDA to document the scientific and regulatory rationale for significant decisions and to meet firm timelines for holding and deciding appeals of such decisions pursuant to 21 C.F.R. § 10.75. Previously, appeals under this regulation had no required timelines and could easily languish for months. The requirement of documenting a rationale unfortunately does not have a deadline matched to the appeal timeline, so that an appeal typically must be filed before the rationale is produced. Also, the “significant decision” threshold excludes some decisions that can have a significant impact on the ability to bring a product to market. For example, although a 510(k) denial is considered a significant decision, an “unable to complete review” letter is not, even though it effectively halts the forward progress of a 510(k) review. For more on the appeals processes, see Center for Devices and Radiological Health (CDRH) Appeals Processes - Guidance for Industry and Food and Drug Administration Staff (May 17, 2013); CDRH Appeals Processes: Questions and Answers About 517A - Guidance for Industry and Food and Drug Administration Staff (July 30, 2014).

²⁹ Medical Device Amendments of 1976, *supra* note 3.

510(k) provisions had “in many ways eclipsed detailed statutory [PMA] provisions so painstakingly drafted.”³⁰

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.³¹ It took FDA a decade (to 1986) to publish a working definition.³² Furthermore, the MDA did not spell out the elements of a workable 510(k) program, perhaps because the 510(k) process was only expected to be transitional. The watershed event for substantial equivalence review from a statutory perspective was the SMDA.³³ The SMDA ratified the 510(k) program as FDA had developed it, and placed it on a sound statutory footing.³⁴

First, the SMDA codified the definition of substantial equivalence that FDA had developed administratively through the experience of clearing devices 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 that the proposed device would be at least as safe and effective as the predicate device. The SMDA also confirmed FDA’s authority to flexibly require preclinical and/or clinical data to support substantial equivalence.

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 review process from 1976 technology and allowed the state of the art to evolve more freely.

Third, the SMDA did not completely give up on regulating Class II devices by FDA-developed performance standards, but issuance of such standards was made optional. This shift was achieved by introducing discretionary “special controls” for Class II devices, which permitted a variety of measures in FDA’s discretion, including but not limited to, performance standards and guidelines for when clinical data is required in a 510(k) submission. The predominant special control FDA applies today is the issuance of guidance documents for the content of 510(k) submissions.³⁵

In 1996, FDA administratively reformed the 510(k) program in a number of ways, streamlining the process and helping to reduce a vexing backlog of 510(k) submissions

³⁰ Jonathan S. Kahan, *Premarket Approval Versus Premarket Notification: Different Routes to the Same Market*, 39 FOOD DRUG COSM. L.J. 510, 510 (1984).

³¹ The legislative history did provide a statement that helped guide development of the concept: “The term ‘substantially equivalent’ is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The committee believes that the term 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. Thus, differences between ‘new’ and marketed devices in materials, design, or energy source, for example, would have a bearing on the adequacy of information as to a new device’s safety and effectiveness, and such devices should be automatically classified into class III. On the other hand, copies of devices marketed prior to enactment, or devices whose variations are immaterial to safety and effectiveness would not necessarily fall under the automatic classification scheme.” H. R. REP. NO. 94-853, at 36-37 (1976).

³² FDA, Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3 (1986).

³³ Safe Medical Devices Act of 1990, *supra* note 20.

³⁴ Ralph F. Hall & Michelle Mercer, *Rethinking Lohr: Does “SE” Mean Safe and Effective, Substantially Equivalent, or Both?* 13 MINN. J.L. SCI. & TECH. 737, 774 (2012) [hereinafter “Hall”].

³⁵ On June 7, 2014, a search of FDA’s device guidance database returned 481 draft and final guidance documents when searched with the term: “Class II Special Controls Guidance Document.”

that had developed.³⁶ These reforms were augmented by statutory improvements enacted in the Food and Drug Administration Modernization Act of 1997 (FDAMA).³⁷ One provision of FDAMA exempted Class I devices from 510(k) review unless intended for a use of substantial importance in preventing impairment of human health or presenting a potential unreasonable risk of illness or injury.³⁸ FDA also was instructed to exempt Class II devices from such review when not necessary to assure safety and effectiveness.³⁹ Today, most Class I devices are exempt from 510(k) clearance and a minority of Class II devices are as well. In the 2009 – 2012 time frame, FDA once again undertook various administrative reforms.⁴⁰

To sum up, the development of the 510(k) pathway based upon substantial equivalence is a story in which FDA officials between 1976 and 1990 made regulatory lemonade out of what was, frankly, a statutory lemon. Congress had overestimated the powers of centralized regulation, imagining that FDA could orchestrate the device industry from Washington with a degree of mastery and subtlety that proved impossible. In particular, the idea that performance standards issued by FDA for hundreds of Class II device types would be the primary method for ensuring their safety and effectiveness was an unworkable failure. It also was impractical to have supposed, as Congress apparently did in 1976, that the resource intensive PMA process (and PDP process) could be widely applied. Fortunately, FDA officials developed the 510(k) provision from an ill-defined transitional measure to the dominant pathway to market for medical devices, and a later Congress had the good sense to ratify it in the SMDA. But for these developments, this country's inventive and vibrant device industry might have been strangled in the crib.

III. CURRENT LEGAL FRAMEWORK

A. *Definition of A Medical Device*

Under the FFDCA,⁴¹ as amended, a “medical device” is defined, in part, as an article, “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease” or “intended to affect the structure or any function of the body” if it “does not achieve its primary intended purposes through chemical action within or on the body . . . and . . . is not dependent upon being metabolized for the achievement of its primary intended purposes.”⁴²

This definition sweeps up an innumerable variety of articles, ranging widely in terms of the type of technology (e.g., design, materials, energy source) and intended use (e.g., diagnostic, therapeutic, surgical, prosthetic). The broad heterogeneity of devices creates a regulatory conundrum, because it is inefficient to apply a one-size-fits all approach,

³⁶ FDA, Final Guidance, *The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications* (Mar. 20, 1998). This guidance created the Abbreviated 510(k) and the Special 510(k).

³⁷ Pub. L. No. 105-115, 111 Stat. 2296 (1997).

³⁸ *Id.* § 206, 111 Stat. at 2339.

³⁹ *Id.*; *Medical Devices; Exemptions From Premarket Notification; Class II Devices*, 63 Fed. Reg. 3142 (Jan. 21, 1998).

⁴⁰ *See* FDA, CDRH Preliminary Internal Evaluations – Volume I, 510(k) Working Group Preliminary Report and Recommendations (Aug. 2010); FDA, CDRH Preliminary Internal Evaluations – Volume II, Task Force on the Utilization of Science in Regulatory Decision-making Preliminary Report and Recommendations (Aug. 2010); IOM Report; FDA, CDRH, *Plan Of Action For Implementation of 510(K) and Science Recommendations* (2011).

⁴¹ Pub. L. No. 75-717, 52 Stat. 1040 (1938).

⁴² FFDCA § 201(h).

but at the same time it is not possible to have an infinitely tailored regulatory regime that adjusts specifically to each device type or subtype.

The variety in devices is often illustrated with a few examples to show the range of risk – e.g., tongue depressors, powered wheelchairs, daily wear contact lenses, pacemakers. However, another good way to understand it is to consider the structure of the premarket review bureaucracy in the CDRH. This organization has been developed to handle the Agency’s perceived premarket review workload, which makes it a good proxy for the variety of device types that FDA must review.

Within CDRH, there are two premarket review offices: the Office of In Vitro Diagnostics and Radiological Health (OIR), which reviews in vitro diagnostic (IVD) and radiological imaging devices, and the Office of Device Evaluations (ODE), which reviews all other devices. Each office has a series of review divisions that oversee review branches. A division corresponds to devices intended for one or more broad medical specialties (e.g., Division of Cardiovascular Devices; Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices), while a branch is more narrowly focused on one or more specific device types (e.g., Circulatory Support Devices Branch; Anesthesiology and Respiratory Devices Branch). ODE is the larger office, with seven divisions encompassing 33 branches. OIR has four review divisions (excluding the Division of Mammography Quality Standards) encompassing 12 branches. Tables depicting these reviewing divisions and branches are set forth in Appendix A.

As another way to understand this variety, consider the classification regulations FDA has promulgated classifying devices by generic type. A “generic type of device” is “a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.”⁴³ FDA has issued more than 1,800 regulations classifying various generic device types.⁴⁴

Even these regulations do not tell the whole story, because they are still quite general (and not all devices have been classified). To further understand the breadth of the devices FDA regulates, consider the three letter product codes FDA has developed to represent specific device types. As of May 14, 2014, there were 6,376 product codes, and the number grows each year.⁴⁵ In some cases, a single product code corresponds to a classification regulation.⁴⁶ In other cases, there may be several codes corresponding to a classification regulation, representing various product subtypes within the same general classification.⁴⁷ Some codes are for unclassified devices.⁴⁸

⁴³ 21 C.F.R. § 860.3(i).

⁴⁴ *Id.* Parts 862-892.

⁴⁵ This figure was provided by FDA staff. Most of these codes may be viewed or downloaded from FDA’s web site. There are some codes in this total that are not on the public web site, but are used for internal FDA purposes. A data file with the publicly available device codes can be downloaded from www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051668.htm.

⁴⁶ *Id.* § 886.4610 (Ocular Pressure Applicator), Product Code LLC.

⁴⁷ *Id.* § 892.5990 (X-Ray Radiation Therapy System), Product Codes IYD, IYH, IYI, IYJ, IYK, IYL, JAD, KPZ, KQA.

⁴⁸ Product Code LXV (Vestibular Analysis Apparatus).

B. *Classification of Devices*

By statute, FDA is entrusted with regulating all of these medical devices.⁴⁹ To triage devices according to risk, the FFDCa creates a tripartite legal classification structure.

Class I devices are exempt from 510(k) review unless FDA determines that a type of device “is intended for a use which is of substantial importance in preventing impairment of human health, or . . . presents a potential unreasonable risk of illness or injury.”⁵⁰ Class I devices are subject to postmarket “general controls” (applicable to all classes) to provide reasonable assurance of safety and effectiveness. General controls applicable to all marketed devices include: establishment registration and device listing; adulteration and misbranding provisions; reporting of certain adverse events, malfunctions and recalls to FDA; and good manufacturing practice (GMP) requirements set forth in the Quality System Regulation.⁵¹

Examples of Class I, 510(k)-exempt devices are:

- tissue processing equipment used to prepare human tissue specimens for diagnostic histological examination;⁵²
- a nasal oxygen cannula used to administer oxygen to a patient.⁵³

Class II devices for which postmarket general controls, by themselves, are not adequate to provide reasonable assurance of safety and effectiveness, but there is sufficient information to develop additional “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 II devices generally require 510(k) clearance, unless FDA has determined for a device type that one “is not necessary to assure the safety and effectiveness of the device.”⁵⁴ As already noted, the primary special controls FDA uses are guidance documents for the content of 510(k) submissions.⁵⁵

Examples of Class II devices requiring 510(k) clearance are:

- an implanted vascular graft prosthesis to repair, replace, or bypass sections of native or artificial vessels, excluding coronary or cerebral vasculature, and to provide vascular access;⁵⁶
- a hemodialysis system used as an artificial kidney system in patients with renal failure.⁵⁷

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

⁴⁹ FFDCa § 513(a).

⁵⁰ *Id.* § 510(l); FDA, Final Guidance, *supra* note 36.

⁵¹ FFDCa § 513(a)(1)(A). For general controls, *see id.* §§ 501, 502; 21 C.F.R. Parts 801, 803, 806, 807, 809, 820.

⁵² *Id.* § 864.3010.

⁵³ *Id.* § 868.5340.

⁵⁴ *Id.* § 510(m)(2).

⁵⁵ *Supra* note 35, and accompanying text.

⁵⁶ 21 C.F.R. § 870.3450.

⁵⁷ *Id.* § 876.5820.

are demonstrated in a PMA application, typically including a clinical trial, advisory panel review, and a pre-approval manufacturing inspection.⁵⁸

Examples of Class III devices requiring PMA approval are:

- dental bone grafting material to fill, augment, or reconstruct periodontal or bony defects of the oral and maxillofacial region if it contains a drug or therapeutic biologic;⁵⁹
- a replacement heart valve to perform the function of any of the heart's natural valves.⁶⁰

C. *Types of Premarket Review*

These three device classes (Class I, II, and III) are the basis for a risk-based approach, tailoring the type of premarket review (or exemption) to the risk posed by a device type. A point too often overlooked is that all three classes reach the market based upon the same standard of “reasonable assurance of safety and effectiveness” determined with reference to the intended use and probable benefit versus probable risk of injury or illness.⁶¹ A riskier Class III device naturally receives more detailed premarket review in order meet the standard, and may have additional postmarket controls. Nonetheless, in all cases, FDA must find that the totality of premarket review and postmarket regulatory controls provide reasonable assurance of safety and effectiveness.

One source of confusion when discussing the statutory scheme is the ambiguity in the word “device.” Depending upon the context, it may refer to a general device type (e.g., a stethoscope) or to an individual instance of a device type (e.g., Firm A’s HeartClearly™ stethoscope). It is important to be as clear as possible about the distinction when discussing the statutory scheme.

FDA has issued a series of regulations classifying device types into Class I, II, or III (codified at 21 C.F.R. Parts 862-892). As mentioned above, there are more than 1,800 of these classification regulations. The classification determination is based upon a generalized risk assessment of the device type. When a firm wishes to market a specific medical device, such as the HeartClearly™ stethoscope, by statutory default it is in Class III, unless FDA issues an order placing it in Class I or Class II.⁶² As a matter of enforcement discretion, however, FDA allows firms to self-assess whether a specific device is within a type that is Class I, 510(k)-exempt. FDA reserves the right to override a self-assessment if it is wrong or exceeds the limitation on 510(k) exemptions built into subsection “.9” of each part of the classification regulations.⁶³

⁵⁸ FFDCa § 513(a)(1)(C); 21 C.F.R. Part 814. FDA’s regulations defining the classes of devices and governing the classification process are in 21 C.F.R. Part 860. FDA has recently proposed amending these regulations to clarify that a device should be in Class III if: (i) it presents known risks that cannot be controlled; (ii) if the risk-benefit profile is unknown or unfavorable; (iii) a full review of manufacturing information is necessary; (iv) premarket review of any change affecting safety or effectiveness is necessary; or (v) it is a combination product with a device primary mode of action (so that CDRH is the lead center), but it includes a drug constituent part for which a finding is required that the drug constituent part is safe and effective or it has a biological product constituent part for which a finding is required that the biological product constituent part is safe, pure, and potent, and such a finding has not been made. Medical Device Classification Procedures, 79 Fed. Reg. 16,252, 16,255-56 (Mar. 25, 2014).

⁵⁹ 21 C.F.R. § 872.3930.

⁶⁰ *Id.* § 870.3925.

⁶¹ FFDCa § 513(a).

⁶² FFDCa §§ 513(f), 515(a).

⁶³ *E.g.*, 21 C.F.R. § 864.9. As another example of self-assessment permitted by enforcement discretion, a device that has not yet received 510(k) clearance (and which is thus technically in Class III) may be exported as a Class I or Class II device if the exporter has a “reasonable expectation that the device could obtain 510(k) marketing clearance in the U.S. if reviewed by the FDA because it is similar in design, construction, and

If the device is not within a Class I type exempt from premarket review, a firm submits a premarket notification (or “510(k) submission”) to demonstrate that a proposed device is substantially equivalent to a non-exempt legally marketed Class I or Class II device. The comparison device is called a “predicate device.” This comparative review performs double duty. First, it is the basis for finding that a proposed specific device is within a device type that is classified as Class I or II. Under the statutory scheme, that finding alone should provide reasonable assurance of safety and effectiveness, because by statutory definition a Class I or Class II device type has such assurance subject to applicable postmarket controls.⁶⁴

Second, the comparative review determines the substantial equivalence of the proposed device to another specific device already determined to be within Class I or II (i.e., the predicate device). Under the FDCA, “substantial equivalence” means:

with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that [FDA] by order has found that the device—

(i) has the same technological characteristics, or

(ii) (I) has different technological characteristics and the information submitted . . . including appropriate clinical or scientific data if deemed necessary by [FDA] . . . demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety or effectiveness as the predicate device.⁶⁵

This definition ties the proposed device to another specific device that FDA has already reviewed, ensuring that they are used for the same purpose and that specific features of the proposed device do not adversely impact safety or effectiveness. This comparison also helps maintain the boundaries of the more general classification definition by ensuring that the technological features of a proposed device do not implicate safety or effectiveness questions that FDA has not reviewed for this device type.

Together, the dual findings from the comparative review are the basis for the ultimate FDA conclusion, required by the FDCA, that there is “reasonable assurance of the safety and effectiveness” of a specific proposed device. As FDA observed in the Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (July 28, 2014) [hereinafter “SE Guidance”]:

. . . 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

intended use to an already-approved or cleared class I or class II device.” FDA, Exporting Unapproved Devices, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ImportingandExportingDevices/ExportingMedicalDevices/ucm346617.htm> (last visited July 13, 2014).

⁶⁴ FDCA § 513(a)(2).

⁶⁵ *Id.* § 513(i).

safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues.⁶⁶

The comparison to a predicate device is an important evidentiary basis for concluding that there is reasonable assurance of the safety and effectiveness of the proposed device. As FDA notes:

Although the 510(k) process involves a comparison of a new device to a predicate device rather than an independent demonstration of the new device's safety and effectiveness, as is required for approval of a PMA, in both cases FDA's review decision reflects a determination of the level of control necessary to provide a "reasonable assurance of safety and effectiveness." The evidentiary standard, however, is different. In the 510(k) context, FDA generally relies, in part, on FDA's prior determination that a reasonable assurance of safety and effectiveness exists for the predicate device. Demonstrating basic similarities between a new device and a predicate device typically requires manufacturers to provide descriptive information such as a comparison of specifications, materials, and technology. In contrast, FDA generally evaluates differences between the new device and the predicate device to determine their effect on safety and effectiveness. It follows that the evidence necessary to show substantial equivalence will increase as differences between the new device and the predicate device increase, if those differences affect, or may affect, safety or effectiveness.⁶⁷

Or, as FDA elsewhere states more succinctly, "the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."⁶⁸ Professor Ralph Hall also has shown in great detail the way in which, as both a legal and practical matter, an evaluation of safety and effectiveness pervades substantial equivalence review.⁶⁹

If FDA finds substantial equivalence, the proposed device is placed in the same class as the predicate device (either Class I or Class II) and subjected to the same or similar general and/or special controls to provide reasonable assurance of safety and effectiveness. If FDA finds that the two devices are "not substantially equivalent" (NSE), then the proposed device remains in Class III and must receive PMA approval, unless the reason for the NSE finding is that the 510(k) submission did not contain sufficient data to make a substantial equivalence determination against the predicate device. In that case, the proposed device could be cleared if a new 510(k) submission is submitted with the missing data.

If a device is NSE because a valid predicate device does not exist, there is one other potential escape from Class III. If FDA agrees that the device type poses a moderate

⁶⁶ SE Guidance at 3-4 (footnotes omitted). The SE Guidance is well worth reviewing for a relatively complete and highly technical description of the SE determination with a number of helpful examples. The SE Guidance does not cover Abbreviated and Special 510(k)s, which raise somewhat different issues, although the legal standard of substantial equivalence is the same. The SE Guidance indicates that FDA will issue a separate guidance for these 510(k) variants. *Id.* at 1.

⁶⁷ *Id.* at 7 (footnote and citation omitted); Hall at 772-78 (demonstrating that the 510(k) system makes a safety and effectiveness determination for each product receiving clearance).

⁶⁸ SE Guidance at 6.

⁶⁹ Hall at 742, 747-51, 753-55, 770-79. See also J. Flaherty, *Defending Substantial Equivalence: An Argument for the Continuing Validity of the 510(k) Premarket Notification Process*, 63 FOOD & DRUG L.J. 901, 914-15 (2008).

level of risk, a request for “de novo” review of the automatic Class III classification for the device type may be filed, requesting development of a new regulation classifying the device type into Class I or Class II.⁷⁰ The de novo marketing authorization is based upon an FDA finding that the classification of this new device type into Class I or Class II satisfies the statutory standard of reasonable assurance of safety and effectiveness, taking into account the intended use and whether the probable benefits of the new device type outweigh the probable risks. This finding requires FDA to consider specific risk mitigation measures that can be employed for the device type, including general and/or special regulatory controls.⁷¹ Risk mitigation measures might include, for example, specific performance testing to be required with each new 510(k) submission.⁷²

A device classified by the de novo procedure becomes a predicate device for future devices within this newly classified type. Going forward, other devices within this type may proceed to market via the 510(k) process. Because most of the classification regulations for Class I and Class II devices were developed in the 1980s for devices on the market as of May 28, 1976, the de novo classification authority is a valuable tool that allows FDA to create new classification regulations for moderate risk device types developed after May 28, 1976.⁷³ The earlier classification regulations were generally developed from an advisory panel’s review of device types without detailed consideration of specific devices. Conversely, the new classification regulations based upon de novo review are generally extrapolated from detailed consideration of specific devices.

As previously mentioned, there is also a category of Class III device types that can be cleared to market via the 510(k) process and which can serve as predicate devices. As of May 28, 1976, all device types on the market automatically became “preamendment Class III,” but were not immediately subjected to premarket approval. Rather, FDA was tasked with issuing classification regulations retaining them in Class III or downclassifying them to Class I or Class II. In the interim, these preamendment Class III device types are cleared to market via the 510(k) process.

It was expected that the classification process would last only a few years. However, it is still not finished. Approximately 24 preamendment Class III device types are still in limbo and continue to be cleared to market via the 510(k) process.⁷⁴ As time goes by, the number continues to dwindle and will eventually reach zero. Consequently, while the risks related to preamendment Class III devices reaching the market via 510(k) review has been a source of practical consternation, it is a transitional problem not relevant to whether substantial equivalence review is an appropriate premarket pathway to ensure the safety and effectiveness of Class I and Class II device types.

⁷⁰ FFDC § 513(f)(2). A de novo request may be requested either within 30 days of an NSE decision on a 510(k) submission or, if the submitter believes there is not a predicate device, the request may be made without submitting a 510(k). FDA may decline the request if it is able to locate an appropriate predicate to place it in Class I or II via the 510(k) process, or if the Agency concludes that the device is not of low-moderate risk, or that general controls are inadequate to control the risks and that special controls cannot be developed.

⁷¹ See FDA, Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications (Mar. 28, 2012), available at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm.

⁷² E.g., Medical Devices; Gastroenterology-Urology Devices; Classification of Pancreatic Drainage Stent and Delivery System, 79 Fed. Reg. 30,722, 30,722-23 (May 29, 2014) (Table 1, listing risks and mitigations).

⁷³ Based on the listing of de novo classifications on FDA’s web site as of May 15, 2014, the de novo process had been used to create classification regulations for 47 new device types.

⁷⁴ See *supra* note 21, and accompanying text.

About two-thirds of the devices entering the market each year (67%) are 510(k)-exempt within either Class I or Class II.⁷⁵ Of the remaining third that require premarket review, about 2% obtain PMA approval or the HDE variant, and 98% obtain 510(k) clearance.⁷⁶ Thus, the 510(k) clearance pathway is by far the dominant pathway to market for devices that undergo premarket review. Within this system, these devices may be iteratively improved, but only within the bounds of substantial equivalence. Device exceeding these bounds will be shunted to the PMA process.

IV. SUBSTANTIAL EQUIVALENCE REVIEW

In each 510(k) review, a proposed device is compared to a predicate device to determine *substantial equivalence*. Under the statutory definition,⁷⁷ a proposed and predicate device must have the same intended use. They may, however, vary in their technological characteristics. As already noted, a determination of substantial equivalence requires that the proposed device be at least as safe and effective as the predicate device, and it may not present different questions of safety or effectiveness. Supporting data to show equivalent safety and effectiveness may include laboratory, animal, and/or clinical testing.⁷⁸

FDA structures each substantial equivalence review by following a flow chart with up to six decision points. This section will look in detail each step in the flow chart from the SE Guidance. For reference, a copy of the flow chart is provided in Appendix B.⁷⁹

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 a predicate device. A legally marketed device may be: (i) a device legally marketed prior to May 28, 1976 (i.e., a preamendment Class III 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 substantially equivalent to another Class I or II device through the 510(k) process or that has been granted de novo classification in Class I or Class II.⁸⁰

In some cases, a submission will cite multiple predicates to exploit several prior clearances, each having variations within the same device type and intended use. The use of multiple predicates allows a proposed device to combine technology previously offered only in separately cleared devices, to have more than one intended use, or to have more than one indication for use under the same intended use. However, the

⁷⁵ IOM Report at 4.

⁷⁶ *Id.* According to FDA staff, as of May 14, 2014, out of 6,376 product codes, 892 represent Class III devices, 2,759 represent Class II devices (176 of these are 510(k)-exempt), 2,247 represent Class I devices (1,991 of these are 510(k)-exempt), and 228 represent unclassified devices. The breakdown does not add to 6,376 due to technical considerations, such as the assignment of codes to convenience kits that combine devices.

⁷⁷ FDCA § 513(i).

⁷⁸ *Id.* § 513(i)(1)(A)(ii)(I) (FDA may require clinical data). See 21 C.F.R. § 807.87 (setting forth information required in a 510(k) submission).

⁷⁹ The flowchart adopted by the SE Guidance is a clarification of the one dating back to the K86-3 Guidance issued in 1986, which was generally the basis for the statutory definition of substantial equivalence enacted in the SMDA. See *supra* note 32, and accompanying text.

⁸⁰ 21 C.F.R. § 807.92(a)(3). This regulation has not been updated to reflect the possibility of de novo classification.

comparison to each predicate device must meet all elements of the statutory definition of substantial equivalence.⁸¹

Decision 2: Does the new device have the same intended use as the predicate device?

FDA's determination of intended use of a device must be based on the proposed labeling submitted in a 510(k).⁸² The focus of the review is the indications for use, but all other information in the proposed labeling may be factored in. The indications for use may differ to a degree between a proposed device and its predicate device, but if the differences are too great, FDA will find that the intended uses are different. If the two devices do not have the same intended use, then FDA must find them NSE.

For purposes of substantial equivalence review, the term *intended use* means the general purpose of the device – what the device accomplishes with its functionality.⁸³ The term *indications for use* usually describes the disease or condition the device is intended to diagnose, treat, prevent, cure, or mitigate, including potentially a description of the patient population for which the device is intended.⁸⁴ For example, the intended use of Biomet, Inc.'s Vanguard™ XP Knee System is the “replacement of a total knee joint and the preservation of the anterior and/or posterior cruciate ligament (ACL/PCL) when used in conjunction with a femoral, tibial and patellar component.”⁸⁵ This intended use describes what the device functionally does. However, the indications for use of this device describe the disease conditions for which it may be used: “1. Painful and disabled knee joint resulting from osteoarthritis, rheumatoid arthritis, or traumatic arthritis where one or more compartments are involved. 2. Correction of varus, valgus, or posttraumatic deformity. 3. Correction or revision of unsuccessful osteotomy, arthrodesis, or failure of previous total joint replacement procedure.”⁸⁶

In some cases, an indication for use describes what the device does rather than the disease, condition, or population it is intended to treat. Such indications for use are referred to as “tool type” indications for use.⁸⁷ For example, the Gyrus ACMI Uro-EZdilate Ureteral Balloon Dilation Catheter is indicated for “dilation of the urinary tract,” which is a function not a disease state. When a device has a tool type indication, the intended use is generally the same as the indication. Thus, the 510(k) summary for the Gymus device describes its intended use and indications identically.⁸⁸

The indications for use of a proposed and predicate device do not have to be identical in order for the two devices to be considered by FDA to have the same intended use. However, in some situations, a difference in the indications raises new safety or effectiveness questions or has the potential to significantly increase an existing safety or effectiveness concern. In such cases, FDA will conclude that the two devices do not have the same intended use. As an example, the SE Guidance posits a proposed device for ablation of cardiac tissue to treat atrial fibrillation. The claimed predicate device is

⁸¹ SE Guidance at 11-13. The SE Guidance provides several examples to illustrate the uses of multiple predicates.

⁸² FFDCRA § 513(i)(1)(E)(i).

⁸³ SE Guidance at 39.

⁸⁴ *Id.* The term “indications for use” is defined in the PMA regulation at 21 C.F.R. § 814.20(b)(3)(i). FDA has a long-standing policy of applying the definition in the same way in the 510(k) context. *Id.* at 16, note 22.

⁸⁵ Vanguard™ XP Knee System, 510(k) Summary, K132873 (Sept. 5, 2013).

⁸⁶ *Id.*

⁸⁷ SE Guidance at 16.

⁸⁸ Gyrus ACMI Uro - EZDilate Ureteral Balloon Dilation Catheter, 510(k) Summary, K132181 (July 12, 2013).

cleared for surgical ablation of cardiac tissue. The proposed and predicate devices both ablate cardiac tissue, and both raise the question of whether that task can be performed safely and effectively. However, the proposed device also claims that the specific ablation pattern achieved (a maze-like pattern that eliminates fibrillatory conduction in the atria) can safely and effectively treat atrial fibrillation. A clinical outcome study would be necessary to evaluate this claim, and there may be additional safety questions associated with the complex lesion being created. Thus, the proposed device would likely be placed in Class III requiring PMA approval.⁸⁹

FDA has some flexibility in defining “intended use.” The point was illustrated in *Cytori Therapeutics, Inc. v. FDA*.⁹⁰ There, Cytori Therapeutics alleged that FDA acted arbitrarily and capriciously by issuing an NSE determination for two devices capable of extracting stem cells from fat tissue. Cytori Therapeutics had compared these devices to predicate devices 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 with greater specificity to include the tissue type. Thus, FDA’s position was that extracting cells from fat is by definition a different intended use than extracting cells from blood, precluding a finding of substantial equivalence. The D.C. Circuit deferred to FDA’s scientific expertise in choosing to distinguish cell extraction based upon tissue type, requiring only that the agency make a determination that is “reasonable and reasonably explained.”⁹¹ With the bar set so low, the court easily found that FDA had met it.⁹²

Decision 3: Does the new device have the same technological characteristics as the predicate device?

A 510(k) submission must identify and compare the various features of the proposed and predicate devices. This information includes an overall description of the device design, materials, energy sources, and other applicable technological features such as software/hardware features, density, porosity, degradation characteristics, nature of reagents (recombinant, plasma derived, etc.), principle of the assay method, and manufacturing-related aspects. FDA will evaluate the submitter’s comparison of the proposed and predicate devices. As observed in the SE Guidance, this comparison may involve both “a comparison of detailed specifications as well as a comparison of the system-level technological characteristics of the devices.”⁹³ If the proposed and predicate devices are shown to have the same technological characteristics, then they will be found substantially equivalent at this point in the review. If not, the review proceeds to the next step.

Decision 4: Do the differences in technological characteristics between the new device and the predicate raise different questions of safety and effectiveness?

Typically, a proposed and predicate device will have at least some differences in technological characteristics. If the proposed device raises different questions of safety

⁸⁹ SE Guidance at 17-18. This example also highlights a sometimes difficult post-market compliance issue. When a device is cleared for broad functionality, to what extent may the manufacturer promote it for specific indications or disease states for which the functionality may be relevant? See FDA, Guidance for Industry: General/Specific Intended Use (Nov. 4, 1998); J. Shapiro, *Promoting Devices for Specific Indications Based Upon A General Clearance*, REGULATORY AFFAIRS FOCUS (Feb. 2003).

⁹⁰ *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922 (D.C. Cir. 2013).

⁹¹ *Id.* at 924.

⁹² *Id.* at 927.

⁹³ SE Guidance at 20.

or effectiveness, then it will be found NSE. A relatively simple example from the SE Guidance illustrates the point. Suppose the predicate device is inserted in the patient's pharynx to provide a patent airway by mechanically moving soft tissue. A proposed device is placed *externally* on the mandible and neck to apply a vacuum to move the soft tissue forward to open the airway. The two devices have the same intended use. However, the predicate device is invasive and does not exert pressure on the vascular, respiratory, or nerve structures of the neck. The proposed device is not invasive but does exert continuous external negative pressure in these areas of the neck, thus raising new types of safety questions regarding risks and potential adverse events associated with stimulation of the nerve structures in the neck. These types of questions were not reviewed for the predicate device. Hence, the two devices are NSE.⁹⁴

Decision 5: Performance Data.

FDA typically accepts descriptive information as sufficient to address Decisions 1 through 4 of the flow chart. At Decision 5, however, FDA typically requires performance data.⁹⁵ Depending upon the device and/or device type, the performance data may be generated by different types of tests and studies to address a wide variety of safety and effectiveness issues.⁹⁶ The SE Guidance also notes that performance data requests may change over time: "For device types with long histories of safe use and well understood mechanisms of action, more limited performance testing data may be sufficient. On the other hand, a pattern of adverse events or published literature documenting poor clinical outcomes with a particular technology may lead FDA to reconsider its regulatory approach to premarket submissions for such technology."⁹⁷

Decision 5a: Are the methods for evaluating the different characteristics' effects on safety and effectiveness acceptable?

In Decision 5a, FDA primarily considers whether there are scientifically valid test methods available to show that the modified technological characteristics are safe and effective. FDA has described its step-wise analytical consideration of the adequacy of the test methods as follows:

FDA . . . considers whether non-clinical performance testing data or analytical studies using clinical samples would be sufficient. For *in vitro* diagnostic devices (IVDs), analytical studies include, but are not limited to, evaluations of accuracy, precision, specificity, and sensitivity. Non-clinical bench performance testing includes a wide variety of test modalities that will be dependent upon the specifics of the actual device, including, but not limited to:

- mechanical, electrical, and biological engineering performance, such as fatigue, wear, tensile strength, compression, flowrate, burst pressure;
- electromagnetic compatibility (EMC);
- sterility;
- stability/shelf life data;
- software validation;
- other forms of non-clinical, including device-specific.

⁹⁴ *Id.* at 21.

⁹⁵ SE Guidance at 22. Another reason for requiring such data is to support performance claims in the labeling. *Id.*

⁹⁶ *Id.*

⁹⁷ *Id.* at 25. See FDA, *SOP: Decision Authority for Additional or Changed Data Needs for Premarket Submissions* (Nov. 9, 2011).

Non-clinical animal and/or biocompatibility studies are typically requested when other forms of non-clinical bench performance testing are not sufficient to demonstrate substantial equivalence.⁹⁸

FDA notes that “manufacturers sometimes direct attention to similar situations FDA has encountered in the past.”⁹⁹ Sometimes a device clearance may be cited, not as a predicate, but because it is relevant “to support scientific methodology or standard references values.”¹⁰⁰ FDA calls these devices “reference devices.”¹⁰¹

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.¹⁰²

FDA currently reports requesting clinical data for fewer than 10 percent of 510(k) submissions reviewed by ODE.¹⁰³ The SE Guidance supplies a number of examples when clinical data may be required. One example illustrates the situation in which a proposed device has the same intended use as the predicate device but new indications require clinical data to establish substantial equivalence:

The manufacturer modifies the indications for use, explicitly or implicitly, by proposing a different surgical implantation method which also affects the indications for use, e.g., a minimally invasive procedure in place of an open procedure, and the safety and effectiveness of the new device cannot be replicated or otherwise characterized in a non-clinical performance (including animal) test environment to adequately support substantial equivalence. . . . Although on its face a minimally invasive procedure would appear to involve less serious risks than an open procedure, the minimally invasive procedure may be less effective or may present different but still serious risks.¹⁰⁴

Another example involves a technological difference: “Suppose a new IVD uses the same analyte-specific chemistry as the predicate, but with a different read-out technology (e.g., chemiluminescence instead of colorimetry). Clinical data may be necessary to demonstrate that the new device performs equivalently to the predicate.”¹⁰⁵

In most cases, there are scientific methods available to bridge the technological gap between the proposed and predicate device, whether laboratory, animal, or clinical. However, if FDA does not agree that the methods are acceptable, an NSE decision will be issued.

⁹⁸ SE Guidance at 25. In actuality, biocompatibility studies are needed more often than this statement implies. Unless a proposed and predicate device have identical patient-contacting materials, or the submitter can show that another cleared device uses the same materials, it is likely that biocompatibility data will be required.

⁹⁹ *Id.* at 13.

¹⁰⁰ *Id.*

¹⁰¹ *Id.* at 13-14. For an example, see note 118, *infra*, and accompanying text.

¹⁰² *Id.* at 23.

¹⁰³ SE Guidance at 23.

¹⁰⁴ *Id.* at 24.

¹⁰⁵ *Id.* at 25.

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 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 present significant laboratory, animal, and/or clinical data running to thousands of pages.¹⁰⁶ FDA now has a 25 page checklist of requirements that must be met just for a 510(k) notification to be administratively accepted for review.¹⁰⁷ The Refuse to Accept (RTA) review lasts up to 15 calendar days.¹⁰⁸

Once a submission is accepted, FDA conducts a substantive review on a 90 calendar day review clock.¹⁰⁹ However, it is typical that partway through the review (e.g., 60 days), FDA will issue an additional information (AI) request.¹¹⁰ The AI request advises a submitter of specific additional data and information (including potentially clinical data) required to find a proposed device substantially equivalent. These requests can be quite significant in terms of the requested data and information. FDA previously allowed 30 days for the submitter's response with extensions granted up to 180 days. However, so many submitters requested extensions that now all are automatically granted up to 180 days to supply requested information. If this deadline is not met, the pending 510(k) is terminated by FDA.

If a response is provided and FDA is unsatisfied with it, an NSE letter will be issued setting forth the remaining deficiencies. The submitter will need to respond in a new 510(k) submission, beginning the process over again. It is not uncommon for a submitter to cycle through the 510(k) process more than once before obtaining clearance.

V. STRENGTHS OF SUBSTANTIAL EQUIVALENCE REVIEW

The 510(k) system applies a common law-style approach to the premarket review of medical devices. After a proposed device is found substantially equivalent, the newly cleared device becomes available as a baseline for future comparison, i.e., as a predicate device. This chain of linked comparisons allows for controlled technological evolution. The approach fits well with the iterative development of most Class I/II device technology. Similar to the common law doctrine of *stare decisis*, prior clearance decisions are generally treated as settled and binding.

On the whole, substantial equivalence review is relatively efficient, because it leverages FDA's prior determinations to narrow the scope of a review. The process is

¹⁰⁶ E.g., J. Bauman, *supra* note 4, at 353; J. Flaherty, *supra* note 69, at 914-15. The courts still characterize a typical 510(k) review as being completed by FDA in 20 hours. E.g., *Lewis v. Johnson & Johnson*, No. 12-4301, 2014 WL 152374 (S.D.W.Va.) at *2, 93 Fed. R. Evid. Serv. 511, PROD. LIAB. REP. (CCH) P 19,310. This 20-hour figure was originally referenced by the Supreme Court in *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 479 (1996), based upon testimony during congressional hearings in 1987. Almost 30 years later, this figure no longer reflects reality and should be considered mythical.

¹⁰⁷ FDA, Guidance for Industry and Food and Drug Administration Staff, Refuse to Accept Policy for 510(k)s (Dec. 31, 2012).

¹⁰⁸ *Id.* at 4.

¹⁰⁹ An abbreviated 510(k) is also reviewed for 90 days. A Special 510(k) has a 30 day review. The review clock starts on the date of submission, and the time spent on the RTA is counted against FDA's deadline. However, the submitter loses the RTA review time if it results in a refusal to accept. The next submission addressing the RTA deficiencies starts over again at time zero.

¹¹⁰ FDA, Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals, at 7 (Oct. 15, 2012).

reasonably predictable, because binding prior clearances act as guideposts to FDA's likely future decision-making. It is adaptable, because there is a heterogeneous body of comparative baselines to match the diversity of devices. And the body of comparative baselines keeps pace with technological innovation in a self-executing manner with each new clearance.

As to the safety and effectiveness of devices emerging from substantial equivalence review, it is worth repeating that they are cleared only if FDA determines that they meet the statutory standard of "reasonable assurance of safety and effectiveness," taking into account substantial equivalence to a predicate device and the postmarket general and special regulatory controls that apply. This statutory standard is the same one applied to Class III devices that must obtain PMA approval.

A. *Efficiency*

In the 510(k) system, a clearance obtained by each market participant is available as a potential building block for a new submission. For example, suppose Firm X obtains clearance for Device A with Feature B, an incremental improvement over all competing technology that does not raise different questions of safety or effectiveness. The predicate device is Device A without Feature B. Firm X provides significant laboratory 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 a substantial equivalence 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 leveraging the prior clearances enables FDA to avoid continually reviewing Feature B and variants as if they were novel.

As another example of efficiency, consider FDA's discussion of when it may allow a "reference device" to be used in a substantial equivalence decision to support scientific methodology or standard references values at Decision 5a in the flow chart. The SE Guidance posits a 510(k) submitted for a total knee implant with a new coating X. There are other coated knee implants already legally marketed, but not with this particular coating. One of the cleared knee implants would be the predicate device. The new coating would not raise different questions – the questions are still whether the coating is biocompatible and whether it impacts implant fixation. The submitter must still show, however, that there are appropriate scientific methods available evaluate the new coating. As it happens, a hip implant has been cleared with the new coating. As FDA puts it:

. . . the manufacturer may refer to . . . the . . . hip implant . . . 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 [hip implant] . . . is used in this case solely to assist with the characterization of the coating on the new device (knee implant with coating X).¹¹¹

Thus, the open regulatory architecture of the 510(k) program enables FDA to efficiently leverage its prior scientific and regulatory determinations. It also enables the various sectors of the device industry to move through the regulatory process more rapidly than any one firm could on its own, each taking advantage of FDA's decisions

¹¹¹ SE Guidance at 14 (footnotes omitted).

in their sector as they steadily improve the technology. The open regulatory architecture does not lessen the rigor of the scientific review, but rather, allows prior relevant FDA determinations to be incorporated.

A commentator has criticized substantial equivalence review as follows:

Focusing on substantial equivalence as opposed to absolute safety and effectiveness . . . leads to inefficient allocation of resources in the area of device safety testing. Device manufacturers are encouraged to design clinical and preclinical tests focusing on the question of substantial equivalence, a question that has little relevance outside of the 510(k) process.¹¹²

Contrary to the foregoing statement, the focus on the delta between proposed and predicate devices is where resources should be directed. In practice, some testing focuses on new features in a proposed device to show that they do not adversely impact safety and effectiveness relative to the predicate device. Other testing is performance testing bearing on typical questions of safety and effectiveness for the device type, and the question will be whether the performance of the proposed device is at least as safe and effective as the predicate device. Thus, the typical 510(k) submission relies on the kind of data and information that logically demonstrate a reasonable assurance of safety and effectiveness. It is not based, as the foregoing statement seems to suggest, upon a strange assortment of tests unconnected to the real world.

The focus on the “delta” is scientifically rational because the elements of safety and effectiveness for most Class I and II devices typically can be disaggregated and considered separately (e.g., biocompatibility, electrical safety, mechanical performance, and sterility). These data can be combined as needed with FDA’s prior review of similar technology, conformance to FDA-recognized voluntary consensus standards,¹¹³ and system-level laboratory, animal, and/or clinical testing. The combined data set provides a solid scientific basis for FDA to determine whether there is reasonable assurance of safety and effectiveness.

The PMA program for approving Class III devices, which does focus on “absolute” safety and effectiveness, is far less efficient, because it does not take advantage of FDA’s prior scientific and regulatory determinations. It has a closed regulatory architecture requiring each applicant to prove its Class III 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.¹¹⁴ A right of reference is not usually granted absent a monetary payment or licensing agreement. It is therefore generally not practical for FDA

¹¹² B. Goldberger, *supra* note 2, at 330 (footnote omitted).

¹¹³ There are voluntary standards developed and maintained by various entities in the United States and around the world, many of which FDA has recognized. FFDCa § 514(c). FDA allows 510(k) submitters to invoke standards to streamline 510(k) submissions and address information needs for substantial equivalence determinations. FDA, 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 as the basis for review of a 510(k) submission. In the first two months of 2013, according to a search of the 510(k) database, there were 471 clearances, of which 14 were Abbreviated 510(k)s.

¹¹⁴ 21 C.F.R. § 814.20(c). A never-invoked statutory provision that would allow data in an existing approval to be used for other approvals after six years has elapsed. *See* FFDCa § 520(h)(4).

to leverage its previous scientific and regulatory determinations even when reviewing similar technology.

A review of “absolute” safety and effectiveness also has a second order problem of determining how safety and effectiveness are to be evaluated. In the absence of a reference point such as a comparator device, this determination can often be quite complex and subjective. A significant portion of the time and effort in a PMA review is often consumed reaching an agreement between the applicant and FDA’s reviewers on the acceptance criteria for preclinical and clinical testing. This problem is especially acute with first-of-a-kind devices. As FDA’s experience and comfort level increases with a specific Class III device type, some burdens ease (e.g., the advisory panel may be omitted) and the data requirements and acceptance criteria become more clearly set.¹¹⁵ Nonetheless, the closed regulatory architecture imposes substantial burdens with each PMA review and slows the pace of innovation. While this burden may perhaps be justified for Class III devices, it most assuredly is not for Class I and Class II devices.

B. Predictability

The FFDCRA does not authorize FDA to disregard a prior clearance. In the 510(k) system, therefore, past substantial equivalence decisions are treated as binding. The legally binding nature of a clearance is critical in providing a reasonable degree of predictability. A firm intent on introducing a new (or modified) device can survey existing clearances and gain a reasonably good understanding of what aspects of the technology FDA has reviewed, what the data requirements were, what conclusions FDA reached, what modifications will potentially raise regulatory concerns (due to the absence of prior FDA review), and what testing may be required to address the concerns.¹¹⁶

This ability to extrapolate the likely regulatory treatment of specific technological innovations allows firms to more quickly and efficiently ascertain regulatory requirements for technological innovations. It also helps mitigate the risk a firm will follow a development trail that leads to a regulatory dead end, in which FDA demands data that cannot be practically supplied or places a device in Class III that is not commercially viable with that classification. These benefits would be lost if FDA had legal authority to disregard or depart from prior clearances at will.

The stability engendered by this aspect of the 510(k) program bears more than a passing resemblance to the common law doctrine of *stare decisis*. As with common law judges, however, FDA reviewers still enjoy substantial discretion in applying prior clearance decisions to the case at hand. As discussed above, the applicability of prior clearances very much depends upon how one characterizes them. The *Cytori Therapeutics* case illustrates that FDA reviewers are adept at distinguishing predicate devices when they wish to do so, not unlike common law judges. *Cytori Therapeutics* also shows that the standard of judicial review is deferential.¹¹⁷

Additionally, FDA reviewers routinely find ways to require 510(k) submitters to address safety or effectiveness problems that have surfaced from postmarket clinical

¹¹⁵ FDA may issue guidance documents spelling out this information or it may become apparent from the public summaries of safety and effectiveness for previously approved devices. FDA, Summary of Safety and Effectiveness Data (SSED), Clinical Section Checklist, Office of Device Evaluation, available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/UCM220929.pdf>.

¹¹⁶ Admittedly, a 510(k) that has been withdrawn before decision or that receives an NSE is not generally available to the public. Thus, some aspects of FDA’s decision-making are not transparent.

¹¹⁷ See also *Ivy Sports Medicine, LLC v. Sebelius*, 938 F. Supp. 2d 47, 59 (D.D.C. 2013) (deferring to FDA’s scientific comparison of proposed and predicate devices).

experience with predicate devices.¹¹⁸ For example, it is not uncommon for reviewers to require data to address concerns that have arisen in adverse event reporting for previously cleared devices of the same type. If, moreover, evidence emerges that a Class II device type is *systemically* riskier than had been supposed, FDA has authority to reclassify it to Class III, retrospectively requiring all 510(k) holders to submit their marketed devices to the PMA approval process. FDA recently issued a proposed order doing just that with surgical meshes for transvaginal pelvic organ prolapse repair.¹¹⁹ This type of reclassification based upon new information is authorized by the FFDCA. Although formerly a cumbersome regulation-based process, FDASIA has now authorized FDA to reclassify devices by administrative order based upon new information, streamlining the process.¹²⁰

In the common law, a precedent that is clearly erroneous can be overruled, at least by a high court. Although precedents are more often distinguished or forgotten than overruled, the ability to correct even rare cases of manifest error is an important part of any administrative or legal system. Under the FFDCA, a device may not serve as a predicate after it has been removed from the market at FDA's initiative, or when it is determined to be misbranded or adulterated by judicial order.¹²¹ FDA also reports administratively rescinding approximately 100 510(k) clearances in the life of the 510(k) program, based upon gross safety issues, procedural irregularity, or fraudulent data. In most cases, FDA has reached agreement with the 510(k) holder regarding rescission.¹²² In 2000, FDA issued a proposed rule to specify when a 510(k) may be rescinded and to standardize procedures for doing so.¹²³ The rule was never finalized. Although there is some uncertainty as the legal standing of FDA-imposed rescissions,¹²⁴ a district court has upheld FDA's inherent authority to rescind a clearance tainted by misconduct, at least if initiated within a reasonable time frame, rejecting an argument that FDA must instead use the statutory reclassification procedures.¹²⁵

C. Adaptability

During 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 device types, including fine variations and minute subtypes, because the body of available comparative baselines consists of all the various devices that have been cleared. Each new clearance enriches

¹¹⁸ See *supra*, note 101 and accompanying text.

¹¹⁹ Reclassification of Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair and Surgical Instrumentation for Urogynecologic Surgical Mesh Procedures; Designation of Special Controls for Urogynecologic Surgical Mesh Instrumentation, 79 Fed. Reg. 24,634 (May 1, 2014).

¹²⁰ FFDCA § 513(e)(1). Under this provision, FDA has had authority since 1976 to reclassify devices by regulation based upon new information. This provision was amended by FDASIA, *supra* note 21, § 608(a) to authorize FDA to reclassify devices by administrative order (rather than regulation) based upon new information.

¹²¹ *Id.* § 513(i)(2).

¹²² *510(k) Rescission Letters Pause as Court Ponders Legality*, FDA REVIEW, July 11, 2014.

¹²³ Medical Devices; Rescission of Substantially Equivalent Decisions and Rescission Appeal Procedures, 66 Fed. Reg. 3523 (Jan. 16, 2001).

¹²⁴ In contrast, there is express authority to withdraw a PMA approval. FFDCA § 515(e), (g). This authority has never been used.

¹²⁵ *Ivy Sports Medicine*, 938 F. Supp. 2d at 55-64. As of this writing, an appeal was pending. *Ivy Sports Medicine, LLC v. Sebelius*, No. 13-5139 (D.C. Cir. filed May 14, 2013).

the baseline and updates it with the latest technology. It is similar to the common law 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. Like the common law, the 510(k) program is self-executing in its management of heterogeneity and the relatively rapid iterative improvement generally associated with device technology.

While any device cleared since 1976 theoretically may serve as a predicate, in practice, the usefulness of predicates tends to fade over time. Of 200 recent clearances sampled, the median age of the predicate devices was just under four and a half years.¹²⁶ 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.

There are situations when the closest predicate or most desirable predicate is not necessarily the most recent. An example would be relatively static device types (e.g., condoms), for which older predicates retain their value. Another example is when automation is generally incorporated in a particular technology, but a submitter seeks to market an older manual version to make it more affordable for health facilities in impoverished or rural areas.

In the more typical case, however, where the goal is to market the latest technology, then a greater disparity between the proposed and predicate devices will work against the submitter by increasing the data required to demonstrate that the changes do not adversely impact safety or effectiveness. Therefore, a submitter in such cases has an incentive to choose the most up-to-date predicate possible in order to take advantage of FDA's prior clearances.

The self-executing ability of substantial equivalence review to keep up with technological change contrasts with a standards-based approach. A consensus standard is typically developed by a committee of experts reaching agreement on "essential" requirements for a device type (e.g., blood pressure cuffs) or performance (e.g., biocompatibility). FDA has statutory authority to recognize consensus standards.¹²⁷ As FDA notes: "Consensus standards provide a consensus approach to certain aspects of the evaluation of device safety and effectiveness, such as testing methods, pass/fail performance criteria, and processes to address areas, such as risk management and usability. The use of consensus standards can also promote international harmonization."¹²⁸

A consensus standard reflects the test methods and device technology in use at the time. However, because it is based upon consensus, it will tend toward the lowest common denominator. Also, a consensus standard begins to decay from the moment of its adoption. It is constantly threatened by technological variation and advance. Thus, FDA recognizes that "[t]here are times when deviations from an FDA-recognized consensus standards are necessary to support the performance and/or claims of the device."¹²⁹ Eventually, the technology varies or evolves so far that a revised standard is

¹²⁶ The sample was constructed from two consecutive series of 100 traditional 510(k) clearances (excluding those without an online summary). The first series started on February 14, 2013 and the second on January 1, 2014. In the combined 200 clearances, 393 predicates were cited with a median age of 53 months (average: 74 months; range: 1 to 353 months).

¹²⁷ 21 CFR § 514(c).

¹²⁸ FDA, Draft Guidance for Industry and Food and Drug Administration Staff, *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices*, at 2 (May 13, 2014).

¹²⁹ *Id.* at 9.

needed, with all the attendant effort and transitional problems of making the switch.¹³⁰ In contrast, the 510(k) baseline accommodates variation and is updated in a self-executing manner as new clearances are granted.

VI. CRITICISM OF SUBSTANTIAL EQUIVALENCE

A. IOM Report

In 2011, FDA asked the IOM to conduct a review of the 510(k) program and report on potential improvements. The IOM Report is a learned and worthwhile summary of the origins, history, and operations of the 510(k) program. After considering all of this information, however, the IOM Report concludes that substantial equivalence review cannot be reformed and should be scrapped.

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

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.¹³¹

Accordingly, the IOM Report concludes (Conclusion 7-1) that the 510(k) process "is not intended to evaluate the safety and effectiveness of medical devices with some exceptions. The 510(k) process cannot be transformed into a premarket evaluation of safety and effectiveness as long as the standard for clearance is substantial equivalence to any previously cleared device."¹³²

This legal conclusion is based upon the 510(k) program as "designed in 1976." To support it, the IOM Report cites *Medtronic, Inc. v. Lohr*,¹³³ which concerned a pacemaker lead cleared in 1982.¹³⁴ The Supreme Court's opinion accurately describes 510(k) review circa 1982; the IOM Report uncritically extrapolates *Lohr* to the present day. The IOM Report also cites older FDA statements prior to enactment of the SMDA (and one legal brief filed by the government in *Lohr*, which likely focused on the statutory scheme circa 1982).¹³⁵ As shown by the SE Guidance discussed above, FDA no longer holds the position ascribed to it in the IOM report. Although the SE Guidance was issued after the IOM Report (and perhaps in response to it), the fact is that FDA's position changed many years ago.

The reason FDA's position changed is that the 510(k) process changed. As discussed above, it evolved into a robust program of premarket review. The IOM Report itself describes the numerous statutory and administrative changes to the 510(k) program, including enactment of a statutory definition of substantial equivalent in the SMDA, but

¹³⁰ *Id.* at 6-7.

¹³¹ IOM Report at xi-xii.

¹³² *Id.* at 5.

¹³³ *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996).

¹³⁴ Hall at 757.

¹³⁵ IOM Report at 36-37.

does not seem to have accepted the implications of these changes for its legal evaluation of substantial equivalence. Instead, the IOM Report analyzes the legal standing of substantial equivalence review based upon an obsolete version of the statutory scheme. This erroneous legal analysis ignores the SMDA and contradicts what regulated firms and legal and regulatory practitioners see daily and know in their bones: every 510(k) review evaluates the safety and effectiveness of the proposed device.

Turning from the legal analysis to practical matters, the IOM Report expresses concern that most Class II devices did not receive a PMA-style evaluation of safety and effectiveness. 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.”¹³⁶ The IOM Report also says: “The committee does not believe . . . that there is a public-health crisis related to unsafe or ineffective medical devices” and “[t]he committee is not suggesting that all, many, or even any medical devices cleared through the 510(k) clearance process and currently on the market are unsafe or ineffective.”¹³⁷

It is not clear whether the IOM Report’s concern is that Class I/II device *types* never received systematic review or that specific devices are not being reviewed adequately as they come to market, or both. Regardless, the grudging concession in the second sentence of Finding 2-1, and the assertion that the IOM Committee is not suggesting that even a single cleared device is unsafe or ineffective, show that this concern is theoretical at best.

In reality, now that 38 years have passed, the cohort of Class I and Class II device types on the market as of 1976 has a long history of clinical use. These device types are generally well-characterized and understood as to their safety and effectiveness and, as might be expected, their technology has been improved substantially over the years. Although the IOM Report denies it, the 510(k) review process decades ago evolved into a safety and effectiveness review of each specific device cleared to market. Regulations requiring reporting of adverse events and recalls to FDA have been in place for decades.¹³⁸ This rich body of clinical and regulatory experience, together with a correct understanding of the 510(k) process as implemented since at least the SMDA, negates any concern that ancient versions of these device types did not undergo a PMA-style review, or that each specific 510(k)-cleared device receives a comparative review rather than a ground-up PMA-style review.¹³⁹ If there were in fact a public health crisis from use of unsafe or ineffective Class II medical devices, FDA (and device users) would know about it. The IOM Report wisely denies that such a crisis exists.¹⁴⁰

B. Recall Study

In the same year as the IOM Report, three researchers published a study of recall data allegedly raising safety concerns about 510(k) cleared devices.¹⁴¹ Specifically, the researchers reviewed 113 Class I recalls (the most serious type) between 2005 and 2009. They found that 21 (19%) of the recalls related to Class III PMA approved devices, 80 (71%) were produced by 510(k) cleared devices, 8 (7%) were from 510(k) exempt

¹³⁶ *Id.* at 32.

¹³⁷ *Id.* at 192, 193.

¹³⁸ *E.g.*, Medical Device Reporting, Final Rule, 49 Fed. Reg. 36,326 (Sept. 14, 1984).

¹³⁹ *See* J. Flaherty, *supra* note 69, at 923.

¹⁴⁰ IOM Report at 6, 193.

¹⁴¹ D. Zuckerman, et al., *supra* note 5.

devices, and 4 (4%) were the result of counterfeit devices not reviewed by FDA. Of the 80 devices that were 510(k) cleared, 13 (12%) were preamendment Class III devices.¹⁴²

Because the percentage of 510(k) cleared devices (71%) responsible for serious recalls was higher than PMA approved devices (19%), the researchers concluded that “PMA standards are clearly superior to 510(k) standards” in ensuring patient safety.¹⁴³ Their claim, however, illogically failed to account for the much greater prevalence of 510(k) cleared devices. If counting the number of serious recalls is to be used as a safety metric, the relevant comparison is the percentage of marketed 510(k) cleared devices responsible for serious recalls versus the percentage of marketed PMA approved devices producing such recalls.

A direct calculation of the respective denominators in these percentages (the prevalence of 510(k) cleared devices and PMA approved devices in the market at the time of the recalls) is virtually impossible. Among other things, a clearance or approval could have been obtained at any number of time points within or prior to the study period and the number of cleared or approved devices actually marketed in the relevant time period is practically unknowable. A good proxy, however, is the IOM Report’s finding that, among devices requiring premarket review, generally 2% obtain PMA approval or the HDE variant, while 98% obtain 510(k) clearance.¹⁴⁴ Even if this estimate is not perfect, it likely captures the relative order of magnitude in the prevalence of marketed, 510(k)-cleared devices versus marketed PMA-approved devices over any significant time period such as the study period from 2005 to 2009.

When this disparity in prevalence is taken into account, it becomes clear that the PMA-approved devices were responsible for a *disproportionate* share of serious recalls between 2005 and 2009. The tiny 2% of PMA approved devices produced 19% of serious recalls in the studied time period. In contrast, the overwhelming 98% of 510(k) cleared devices were responsible for only 71% of serious recalls.

Additionally, the study put the 12% of serious recalls attributable to preamendment Class III devices on the 510(k) side of the ledger. These devices have received 510(k) clearance since 1976 as a transitional measure while awaiting an FDA regulation retaining them in Class III or downclassifying them to Class I or Class II. The researchers singled out one of these devices, automated external defibrillators (AEDs), as responsible for most of the 12% of recalls generated by preamendment Class III devices. In 2013, FDA issued a proposed rule retaining AEDs in Class III and requiring PMA approval.¹⁴⁵

It may be appropriate to criticize FDA for not making this decision sooner, but it is illogical to criticize substantial equivalence review categorically because of serious recalls associated with AEDs. Substantial equivalence review is intended for Class I and Class II devices, not Class III devices like the AEDs. Eventually, there will be no more preamendment Class III devices receiving 510(k) clearance. In this study, which purports to compare the intrinsic relative safety of the 510(k) and PMA standards, all recalls attributable to preamendment Class III devices should have been excluded from the analysis. If that had been done, the recalls attributable to 510(k)-cleared devices would have been 59% rather than 71%.

With these revised numbers (whether 59% or 71%), the conclusion of this study is turned on its head. *If* one believes (as the authors of the study clearly do) that a valid metric for comparing the safety of 510(k) clearance versus PMA approval is to count

¹⁴² *Id.* at 1008-09.

¹⁴³ *Id.* at 1009.

¹⁴⁴ IOM Report at 4.

¹⁴⁵ Effective Date of Requirement for Premarket Approval for Automated External Defibrillator System, 78 Fed. Reg. 17,890-02 (Mar. 25, 2013).

the relative percentages of serious recalls associated with each review process, the study actually shows that 510(k) standards are *superior* to PMA standards and not the other way around.¹⁴⁶

VII. IMPROVEMENT IN 510(K) TRANSPARENCY

For the 510(k) program to operate with maximum predictability, the public 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 allow a sponsor seeking clearance of a proposed device to hunt for predicate devices, learn FDA's existing data requirements, and reliably extrapolate likely additional data requirements that might apply to a proposed device.

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 and use. Unfortunately, the evolution of regulatory requirements often is not well publicized, and so 510(k) applicants are too frequently 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 transparent enough to allow prospective applicants to accurately extrapolate new or additional requirements.

An important hindrance to transparency is 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. It contains summaries of the 510(k) decisions that are supposed to provide information about the proposed and predicate devices, and the supporting data and conclusions to be drawn from it.¹⁴⁷ However, these summaries are not easily full text searchable. Furthermore, even if they were, the summaries are prepared by the submitter. They tend to be deliberately vague about the testing and information submitted to obtain clearance, and they generally reveal little about FDA's review.

In recent years, FDA has gotten better about policing the quality of these summaries. The SE Guidance, for example, devotes an entire section and two appendices to communicating FDA's expectations in this regard.¹⁴⁸ Even so, another problem is that 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.¹⁴⁹ This option makes detailed information about the clearance virtually impossible to obtain in an electronic search, and FDA historically has not provided meaningful enforcement if the submitter fails to comply.

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

¹⁴⁶ The study does not actually establish that the observed difference in recall rates is caused by differences in the 510(k) versus PMA process. Rather, the study assumes such causation, and then with circular logic concludes that the observed difference establishes the greater safety of the PMA process. Also, a proper study would define the potential variables that could cause a difference in recall rates (e.g., Class III devices are by definition riskier) and then control for them in order to isolate the causal role of the premarket review process. That was not done here.

¹⁴⁷ 21 C.F.R. § 807.92.

¹⁴⁸ SE Guidance at 26, Appendix B, Appendix C.

¹⁴⁹ 21 C.F.R. § 807.93.

important decision data unnecessarily impedes a full understanding of prior clearance decisions. To truly understand relevant clearance history, it sometimes may be necessary to submit Freedom of Information Act (FOIA) requests to FDA, which are filled in an uncertain time frame ranging from months to years. In some cases, private companies may have obtained the documents and made them available online for a fee of several hundred to several thousand dollars. However, it is fairly random as to whether these companies will have obtained the desired clearances.

This issue may seem relatively insignificant. 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 while deciding new cases. At the same time, suppose litigants and their counsel only have access to a different database with case squibs, not entire decisions; the squibs are written by the prevailing litigants, the database is partially indexed, and 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 ranging from months to years.

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 ready access to the decision and the supporting facts and analysis in prior cases.

An important step toward greater transparency is readily available. Since 2004, without much fanfare, the OIR has been publishing "decision memoranda" on which its 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 are reviewed by the ODE, which does not publish its decision memoranda. However, ODE reviewers already prepare a memorandum to justify clearance decisions. The simple posting of these memoranda in the 510(k) database would greatly improve the 510(k) system.

It would not be necessary to undertake a grand project to impose a standard format on ODE's 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 made capable of easy full text searching like that offered by Westlaw and LEXIS/NEXIS with respect to court decisions and other legal documents. With so much of the treatment of proposed devices hinging on FDA's prior clearance decisions, it is important for FDA to make public access to these decisions as easy as possible. It would be most 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 AI

request describing deficiencies in the submitted information. This correspondence itself is a valuable window into requirements that may apply.

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) and available for immediate downloading. Of course, there are obstacles. Perhaps most challenging, all files must be redacted for trade secret and commercial confidential information. But FDA could modify its FOIA program to require submitters to redact their 510(k) submissions and associated correspondence upon receiving clearance or soon after. FDA could then review and modify the redactions as appropriate (which they currently do anyway when responding to FOIA requests).¹⁵⁰

The decision memoranda must be redacted, too. To speed the process, FDA could dedicate FOIA staff to this task. It also might be feasible to alter decision memoranda to the limited extent of requiring that all redactable information be placed in an initial summary section that would be automatically redacted. FOIA staff then would simply need to review the remainder of a decision memorandum for stray redactable information.

If creating a searchable/downloadable database is technologically challenging, an interim approach would be to establish a short, predictable timeline for providing these same files pursuant to individual FOIA requests. There is no reason that 510(k) requests must be in the same queue as all other FOIA requests. A special program could be administratively established to fast track these requests in a separate queue. In short, there are many potential solutions to the challenges of greater transparency, but the effort must be made. So far, an adequate effort has not been made.

VIII. CONCLUSION

The erroneous belief that substantial equivalence review does not address safety and effectiveness was reinforced by the first major judicial pronouncement on the 510(k) pathway, which was the Supreme Court's 1996 decision in *Medtronic, Inc. v. Lohr*. This decision concerned a device cleared in 1982. Courts and commentators since *Lohr* (including the Supreme Court itself) have erred in uncritically extrapolating *Lohr* to the present day, and ignoring far-reaching statutory and administrative changes in substantial equivalence review.¹⁵¹ A sound description of the 510(k) program *must* start with the statutory requirements *after* the SMDA and perhaps even after FDAMA, but certainly not the period between the original MDA and the SMDA. Any discussion of the 510(k) program that relies on *Lohr* (or subsequent uncritical citations to it) is mischaracterizing the statutory basis for the 510(k) program. The IOM Report is an example of criticism that perpetuates this error.

Some criticism of the 510(k) program, like the recall study discussed above, fails to distinguish between preamendment Class III devices cleared to market via the 510(k) process and Class I and Class II devices. It is understandable that a supposedly transitional measure lasting for almost half a century could look like a permanent feature of the system. But the fact is that substantial equivalence review has proven well suited to Class I/II devices. It is not valid to criticize substantial equivalence review for issues relating to preamendment Class III devices that potentially should have been subject to PMA approval long ago. Any criticism of the 510(k) program that elides this vital distinction should be categorically rejected.

¹⁵⁰ *Id.* § 20.22

¹⁵¹ Hall at 774.

After calling for substantial equivalence review to be scrapped, the IOM Report lists the attributes that a replacement system should have. These attributes include a process based on sound science; predictable, straightforward, and fair; self-sustaining and self-improving; capable of facilitating innovation; applying relevant appropriate authorities and standards throughout the life cycle of devices to ensure safety and effectiveness; and risk-based.¹⁵² This article has suggested that substantial equivalence review actually satisfies these requirements. It is based on sound science; the method of case-by-case review in light of binding precedents generally leads to a predictable and self-sustaining process; and FDA's determinations apply a risk-based approach to finding assurance of safety and effectiveness based upon premarket review and postmarket regulatory controls. The tremendous advance in medical device technology in the past few decades, including Class I/II devices, suggests that substantial equivalence review facilitates (or, at least, does not hinder) robust innovation. In short, the 510(k) process has all or almost all of the attributes that the IOM Committee suggests should be incorporated in a premarket review system for moderate risk devices.

Of course, this article's defense of substantial equivalence review does not mean that the *status quo* is untouchable. For example, Section VII, above, discusses the need for improved public access to the basis and reasoning of each substantial equivalence decision. But a replacement effort for the entire system would be costly and the results uncertain. It took decades of experience to develop substantial equivalence review into a reasonably satisfactory process. It would undoubtedly take decades more to design a new system, transition to it, and resolve its inevitable growing pains. There is no need to embark on such an uncertain voyage. The current system of substantial equivalence review is sound and should be retained. By engaging in targeted reform rather than wholesale condemnation, it can be made better.

¹⁵² IOM Report at 9.

APPENDIX A

PREMARKET PRODUCT REVIEW BUREAUCRACY

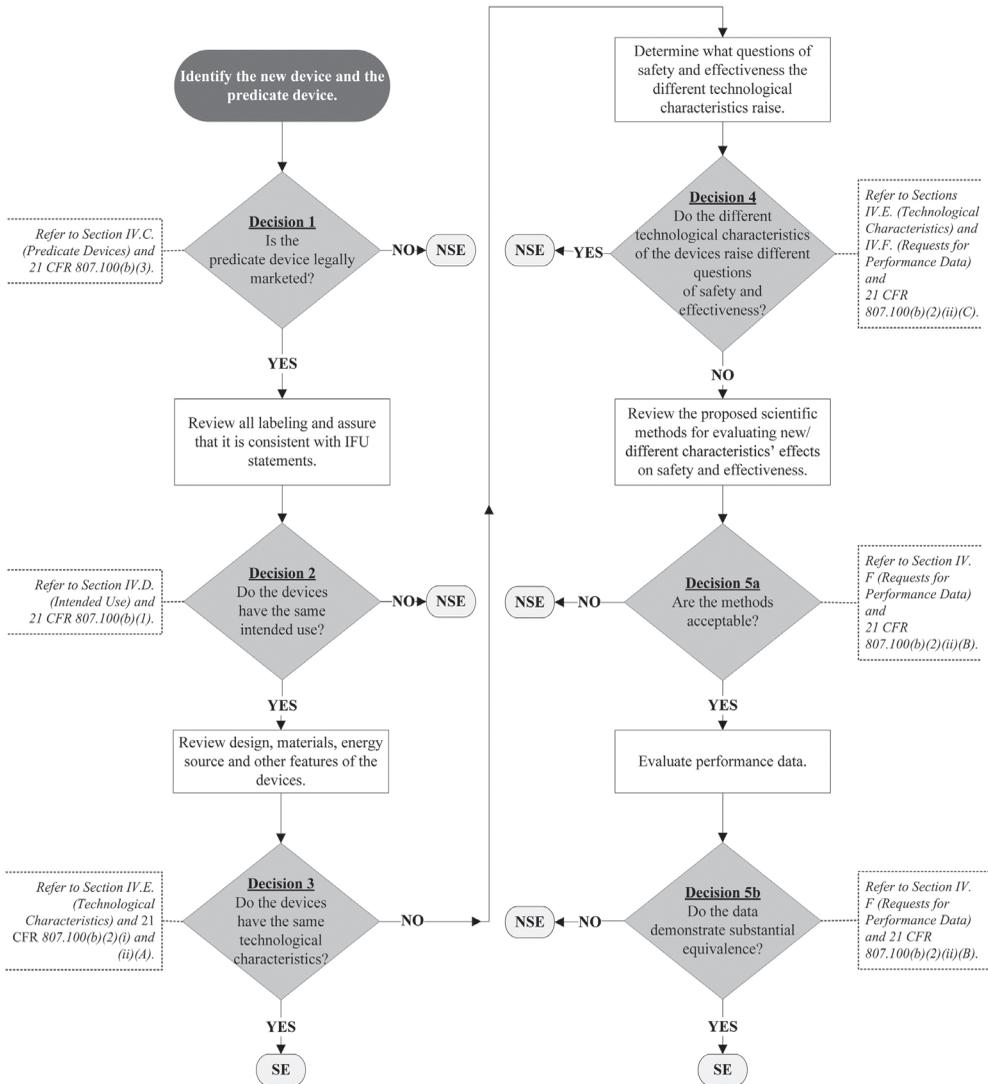
Office Of Device Evaluation							
Review Divisions	Anesthesiology, General Hospital, Respiratory, Infection Control, And Dental Devices (DAGRID)	Cardiovascular Devices (DCD)	Ophthalmic and Ear, Nose, and Throat Devices (DOED)	Neurological and Physical Medicine Devices (DNPMD)	Orthopedic Devices (DOD)	Surgical Devices	Reproductive, GastroRenal, and Urological Devices (DRGUD)
Subordinate Review Branches	Anesthetic Devices (ADB) General Hospital Devices (GHDB) Respiratory Devices (RPDB) Infection Control Devices (INCB) Dental Devices (DEDB)	Cardiac Diagnostics Devices (CDDB) Cardiac Electrophysiology Devices (CEDB) Circulatory Support Devices (CSDB) Interventional Cardiology Devices (ICDB) Implantable Electrophysiology Devices (IEDB) Peripheral Interventional Devices Branch (PIDB) Structural Heart Devices (SHDB) Vascular Surgery Devices (VSDB)	Contact Lenses and Retinal Devices (CLRD) Diagnostic and Surgical Devices (DSDB) Intraocular and Corneal Implants (ICIB) Ear, Nose, and Throat (ENTB)	Neurostimulation Devices (NSDB) Neurodiagnostic and Neurosurgical Devices (NNDDB) Physical Medicine Devices (PNDB)	Joint Fixation Devices One (JFDB1) Joint Fixation Devices Two (JFDB2) Restorative and Repair Devices (RRDB) Anterior Spine Devices (ASDB) Posterior Spine Devices (PSDB)	General Surgery Devices One (GSDB1) General Surgery Devices Two (GSDB2) Plastics and Reconstructive Surgery Devices One (PRSB1) Plastics and Reconstructive Surgery Devices Two (PRSB2)	Obstetrics/ Gynecology Devices (OGDB) Urology and Lithotripsy Devices (ULDB) Renal Devices (RNDB) Gastroenterology Devices (GEDB)

OFFICE OF IN VITRO DIAGNOSTICS AND RADIOLOGICAL HEALTH

Review Divisions	Chemistry and Toxicology Devices (DCTD)	Immunology and Hematology Devices (DIHD)	Microbiology Devices (DMD)	Radiological Health (DRH)
Subordinate Review Branches	Chemistry Diabetes Toxicology	Hematology Immunology and Flow Cytometry	General Viral and Hepatitis General Bacterial and Antimicrobial Susceptibility Bacterial Respiratory and Medical Countermeasures	Magnetic Resonance and Electronic Products Diagnostic XRay Systems Nuclear Medicine and Radiation Therapy Mammography, Ultrasound and Imaging Software Branch

APPENDIX B*

510(k) DECISION-MAKING FLOWCHART Contains Nonbinding Recommendations



SE = "Substantially Equivalent"
NSE = "Not Substantially Equivalent"
IFU = "Indications For Use"

This Flowchart is not intended to be used as a 'stand-alone' document and should only be considered in conjunction with the accompanying text in this guidance.

* Food and Drug Administration, Guidance on the 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (July 28, 2014).