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CDRH PRELIMINARY INTERNAL EVALUATIONS – VOLUME I

510(k) Working Group

Preliminary Report and Recommendations

August 2010

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Center for Devices and Radiological Health

U.S. Food and Drug Administration

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1. EXECUTIVE SUMMARY

The Center for Devices and Radiological Health (CDRH or the Center) within the Food and Drug Administration (FDA) is responsible for assuring that marketed medical devices provide a reasonable assurance of safety and effectiveness, and for assuring the safety of radiation-emitting products.[1] With the exception of certain lower-risk devices that are exempt from premarket review, CDRH reviews the safety and effectiveness of medical devices for their intended use prior to marketing. Under the premarket approval (PMA) process, each manufacturer must independently demonstrate reasonable assurance of the safety and effectiveness of its device for its intended use. Under the premarket notification (510(k)) process, CDRH will clear a new device if it finds, through review of a 510(k) submission, that the device is substantially equivalent to a predicate. Generally, predicate devices, as largely class II devices, are those for which there is a reasonable assurance of safety and effectiveness with general and applicable special controls.

Since its establishment in 1976, the 510(k) process has undergone a number of statutory changes. In addition, FDA has modified its implementation of the process to adapt to changing circumstances and to accommodate the evolving medical device landscape.[2] The current 510(k) program reflects the current statutory framework and FDA's implementation of that framework through regulation, guidance, and administrative practice.

The 510(k) program, as it currently exists, is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that are safe and effective, and fostering innovation in the medical device industry. In recent years, concerns have been raised within and outside of FDA about whether the current 510(k) program optimally achieves these goals.

The 510(k) Working Group (the Working Group) was convened in September 2009 as part of a two-pronged, comprehensive assessment of the 510(k) process. The other component of this assessment is an ongoing independent study by the Institute of Medicine (IOM) that is expected to conclude in the summer of 2011. The 510(k) Working Group was charged to evaluate the 510(k) program and explore actions CDRH could take to strengthen the program and improve the consistency of its decision making, with a principal focus on actions the Center could take in the short term under its existing statutory authority.

The Working Group was comprised of representatives from across the Center. It consisted of 10 subgroups, each of which was assigned a particular area of focus within the broader 510(k) framework. As part of its assessment, the Working Group gathered input from CDRH employees and managers (*hereinafter* staff or review staff) and a range of external constituencies on how the 510(k) process currently operates, what challenges it presents for CDRH staff and others, and what steps the Center might take to improve the program. The Working Group also collected and analyzed relevant data from CDRH's internal databases to identify trends in the review of various types of 510(k) submissions, as well

[1] Some medical devices (namely, those related to the diagnosis of retroviruses such as HIV, and those related to blood, human tissue, and cellular products) are under the jurisdiction of FDA's Center for Biologics Evaluation and Research (CBER). This document pertains only to CDRH.

[2] *See* Section 4 of this report for a discussion of the 510(k) program's inception and evolution, including major legislative, regulatory, and administrative milestones.

as postmarket trends related to devices reviewed through the 510(k) process.[3] This preliminary report is the product of the Working Group's efforts.

1.1. Overview of Findings and Recommendations

The recommendations contained in this report are preliminary. FDA has not made any decisions on specific changes to pursue. FDA is soliciting public input on the recommendations discussed in this report, including the feasibility of implementation and potential alternatives. Once its assessment of public input and other necessary reviews are completed, FDA will announce which improvements it will implement, as well as projected timelines for implementation. There may be proposed changes that the Center will refer to the Institute of Medicine for further review.

As described above, the aim of the 510(k) program is two-fold: (1) to assure, through a quality review process, that marketed devices, subject to general and applicable special controls, provide a reasonable assurance of safety and effectiveness; and (2) to foster innovation. Robust premarket review is an essential component of CDRH's medical device oversight. CDRH's postmarket tools, while valuable, have important limitations and are not sufficient to serve as a substitute for high-quality premarket review. At the same time, in order to facilitate innovation, the premarket clearance process must be reasonable and predictable.

An effective 510(k) program is predicated on three major elements. First, 510(k) decision making must be grounded in a rational, well-defined, and consistently interpreted review standard. Second, the 510(k) program must support informed decision making by facilitating the collection of sufficient information to allow for well-informed, reliable decisions, and by providing an operational infrastructure and tools that enable FDA to make the best use of that information through knowledge-development and knowledge-sharing. Third, there must be appropriate systems and metrics in place to continuously assure quality, consistency, timeliness, and predictability, to the extent feasible, across the 510(k) program.

The 510(k) Working Group identified several areas for improvement related to each of these elements.

With regard to the 510(k) review standard, the Working Group found that key terms in the statutory definition of "substantial equivalence" have not been consistently interpreted by the Center. In particular, there is insufficient clarity about what constitutes the same versus a new "intended use," and about when "different technological characteristics" raise "different questions of safety and effectiveness." Ambiguity at these critical decision points, at times, has contributed to inconsistency in CDRH's 510(k) decision making. As the 510(k) standard has been applied to a wider range of devices over time, including increasingly varied, complex, and potentially higher-risk technologies, the need for greater clarity with respect to these terms has become even more pressing. The Working Group recommends that CDRH more clearly define these terms in guidance and training for review staff and industry.

Further, while the concept of "substantial equivalence to a predicate" is generally reasonable, CDRH's application of this standard has, in certain cases, raised concerns. When a predicate has a well-established risk/benefit profile and is generally well-regarded by the health care community, a premarket comparison of a new device to that predicate, with sufficient information, can provide reasonable assurance that the device, subject to general and applicable special controls, is safe and

[3] *See* Section 3 of this report for a discussion of the 510(k) Working Group's structure and methods.

effective for its intended use. However, concerns have been raised that current FDA regulations and practice may allow for some types of predicate comparisons that are insufficient to *consistently* provide such assurance, including the use of predicates that have been withdrawn from the market due to issues of safety or effectiveness and the use of so-called "split predicates," a term that refers to using one predicate as the basis for a comparison with respect to "intended use" and another predicate as the basis for a comparison with respect to "technological characteristics." The use of a "split predicate" is akin to combining different attributes of more than one device into a single, nonexistent predicate device whose risks and benefits are unknown. The Working Group recommends that CDRH consider taking steps, through guidance, to set forth factors regarding when a device should not be used as a predicate. Such factors should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered. The Working Group also recommends that CDRH explore the possibility of explicitly disallowing the use of "split predicates."

In addition to defining the 510(k) review standard more clearly, it is important for CDRH to use the tools it has to provide an appropriate, risk-based level of regulatory control for devices that are determined not to have a valid predicate but whose risks do not warrant a premarket approval approach. The process for Evaluation of Automatic Class III Designation, also known as the de novo classification process, is meant to serve as an alternative regulatory pathway for such devices; however, as currently implemented, it is inefficient and has not been optimally utilized across the Center. The Working Group therefore recommends that CDRH take steps to streamline its implementation of the de novo process and to assure that it is utilized appropriately across the Center.

With regard to informed decision making, the Working Group found that it is challenging for review staff to obtain, in an efficient and predictable manner, sufficient device information to make well-supported decisions. To obtain such information without creating unnecessary delays and burden, CDRH must provide submitters with as much up-front clarity as feasible about its evidentiary expectations. The Working Group therefore recommends that CDRH take steps to foster the submission of high-quality 510(k) device information, in part by better clarifying its expectations for 510(k) content.

Most notably, the Working Group recommends that CDRH explore the possibility of developing guidance to define, as a heuristic, a subset of class II devices called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would typically be necessary to support a substantial equivalence determination. Delineating between "class IIa" and "class IIb" would not reconfigure the current, three-tiered device classification system established by statute; it would represent only an administrative distinction. The development of a "class IIb" guidance would provide greater clarity regarding what submitters would generally be expected to provide in their 510(k)s for certain types of devices. Although further deliberation would be needed to better characterize "class IIb," potential candidates for this device subset may include implantable devices, life-sustaining devices, and life-supporting devices, which present greater risks than other class II device types.

The Working Group found that, in general, most instances where concerns were raised by industry and Center staff about problems with the 510(k) program involved the small subset of devices for which staff requested clinical information, either to answer questions appropriate for a substantial equivalence determination, but sometimes in cases where the sponsor had no advance notice that such information would be needed, or to answer questions more appropriate for the de novo classification process. Both scenarios have contributed to less predictability and longer time-to-decision in the 510(k) program. By

creating a "class IIb" device subset and making appropriate use of a streamlined de novo process, CDRH could make more predictable, timely, and consistent decisions.

The Working Group also found that limitations in CDRH's information technology and knowledge management infrastructure and tools make it difficult for Center staff and external parties to readily access meaningful information that would help improve both the quality and the predictability of 510(k) decision making. Because 510(k) decision making relies on a comparison to a predicate, review staff and submitters must have an adequate level of familiarity with predicate devices and past 510(k) decisions, supported by well-organized and easily accessible information, in order for the process to function properly. The Working Group therefore recommends that CDRH enhance its internal and public 510(k) databases to provide more complete, up-to-date device information to review staff and the Center's external constituencies.

Finally, the Working Group found that there is a need for more robust systems and tools for quality assurance in the 510(k) program. Quality and consistency depend on a highly qualified, well-trained, and well-supported review staff, and on appropriate oversight. The Working Group therefore recommends that CDRH enhance its support for training and professional development for review staff. Further, currently there are insufficient tools and metrics in place to assess the consistency of decision making across the 510(k) program, and to track the program's public health impact quantitatively. Although CDRH collects information on device performance in the postmarket setting, important limitations, including the inability to consistently link postmarket events to specific 510(k)s, make this information, in isolation, an unreliable measure of program effectiveness. The Working Group recommends that CDRH develop program metrics and better systems for continuous monitoring of 510(k) program performance and effectiveness, in part through the oversight of a new Center Science Council comprised of experienced reviewers and managers, under the direction of the Deputy Center Director for Science.

The Working Group's findings and recommendations are outlined on the following pages and discussed in greater detail in Section 5 of this report. Terms used in the box below are explained in the body of the report. Additional information about the group's work, including a summary of staff and public input, is provided in the Appendices.

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Overview of Findings and Recommendations

1. A Rational, Well-Defined, and Consistently Interpreted Review Standard

» **Finding:** There is insufficient clarity with respect to pivotal terms in the definition of "substantial equivalence."

Recommendation: CDRH should clarify the meaning of "substantial equivalence" through guidance and training for reviewers, managers, and industry.

- ***"Same Intended Use"***
  - **Lack of a Clear Distinction Between Terms**
    - The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in "intended use." The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new "intended use." Therefore it recommends that CDRH carefully consider what characteristics should be included under the term "intended use," so that modifications that are currently considered to be only changes in "indications for use" and that CDRH determines do not constitute a new "intended use," are not in the future necessarily construed as changes in "intended use" merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of "intended use" more restrictive. The Center should also carefully consider what it should call the existing "Indications for Use" statement in device labeling and the "Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.
  - **Insufficient Guidance for 510(k) Staff and Industry**
    - The 510(k) Working Group recommends that CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of "intended use."
    - The 510(k) Working Group further recommends that CDRH provide training for reviewers and managers on how to determine "intended use." Such training should clarify the elements of a device application that should be considered when determining the "intended use," *e.g.*, product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on "intended use" should also be provided to industry.

- **Off-Label Use**
  - The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(1)(E) of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(i)(1)(E)) that would provide the agency with express authority to consider an off-label use, in certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process. Such circumstances would include the availability of compelling evidence that the primary use of the marketed device will be off-label. If the Center were to pursue such an approach, it should also clearly define what type and level of evidence would be sufficient to determine that the off-label use is the primary intended use.

- ***"Different Questions of Safety and Effectiveness"***
  - **Inconsistent Terminology**
    - The 510(k) Working Group recommends that CDRH reconcile the language in its 510(k) flowchart (shown on page 27 of this report) with the language provided in section 513(i) of the Federal Food, Drug, and Cosmetic Act (21 USC §360c(i)) regarding "different technological characteristics" and "different questions of safety and effectiveness."
  - **Insufficient Guidance for 510(k) Staff and Industry**
    - The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise such questions (*e.g.*, a change in energy source, a different fundamental scientific technology).
    - The 510(k) Working Group further recommends that CDRH develop and provide training for reviewers and managers on how to determine whether a 510(k) raises "different questions of safety and effectiveness." Training on "different technological characteristics" and "different questions of safety and effectiveness" should also be provided to industry.

» **Finding:** CDRH's current practice allows for the use of some types of predicates that may not be appropriate.

Recommendation: CDRH should explore the development of guidance and regulation to provide greater assurance that any comparison of a new device to a predicate is valid and well-reasoned.

- ***Concerns about Predicate Quality***
  - The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.

- ***Rescission Authority***
  - The 510(k) Working Group recommends that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.

- ***Use of "Split Predicates" and "Multiple Predicates"***
  - The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate, explaining when "multiple predicates" may be used. The Center should also explore the possibility of explicitly disallowing the use of "split predicates." In addition, CDRH should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices (described in Section 5.1.2.3 of this report) and bundled submissions (described in Section 4.3.4.2).
  - The 510(k) Working Group recommends that CDRH provide training for reviewers and managers on reviewing 510(k)s that use "multiple predicates," to better assure high-quality review of these often complex devices. This training should clarify the distinction between multi-parameter or multiplex devices and bundled submissions. In addition, CDRH should more carefully assess the impact of submissions for multi-parameter or multiplex devices and bundled submissions on review times, and should consider taking steps to account for the additional complexity of these submissions as it establishes future premarket performance goals.
  - The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports, as shown in Section 5.1.2.3 of this report.

» **Finding:** Although there exists an alternative regulatory pathway for devices that lack a clear predicate but whose risks do not warrant class III controls (*i.e.*, the process for Evaluation of Automatic Class III Designation, also known as the de novo classification process), this pathway, as currently implemented, is inefficient and has not been utilized optimally across the Center.

Recommendation: CDRH should reform its implementation of the de novo classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control for eligible devices.

- The 510(k) Working Group recommends that CDRH revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for de novo classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing a generic set of controls that could serve as baseline special controls for devices classified into class II through the de novo process, and which could be augmented with additional device-specific special controls as needed.

2. Well-Informed Decision Making

» **Finding:** It is challenging for CDRH to obtain, in an efficient and predictable manner, the information it needs to make well-supported premarket decisions and assure that each new or modified 510(k) device is substantially equivalent to a valid predicate.

Recommendation: CDRH should take steps through guidance and regulation to facilitate the efficient submission of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new "class IIb" device subset.

- ***Unreported Device Modifications***
  - The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).
  - The 510(k) Working Group further recommends that CDRH explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not warrant a new 510(k). The Center could consider phasing in this requirement, applying it initially to the "class IIb" device subset described below, for example, and expanding it to a larger set of devices over time.

- ***Quality of Submissions***
  - **Lack of Clarity**
    - The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported. If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.
    - The 510(k) Working Group further recommends that CDRH explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device's key features. Currently, CDRH receives photographs *or* schematics as part of most 510(k)s; however, receiving both as a general matter would provide review staff with more thorough information without significant additional burden to submitters. Further, CDRH could include photographs

and schematics, to the extent that they do not contain proprietary information, as part of its enhanced public 510(k) database, described below, to allow prospective 510(k) submitters to develop a more accurate understanding of potential predicates. Exceptions could be made for cases in which a photograph or schematic of the device under review will not provide additional useful information, as in the case of software-only devices. CDRH should also explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for CDRH to access upon request, so that review staff could, as needed, examine the device hands-on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.

- **Improper Use of Recognized Standards**
  - The 510(k) Working Group recommends that CDRH provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation within a 510(k). CDRH should also consider revising the requirements for "declarations of conformity" with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity if they choose to make use of a "declaration of conformity."
- **Incomplete Information**
  - The 510(k) Working Group recommends that CDRH consider revising 21 CFR 807.87, to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review.

- ***Type and Level of Evidence Needed***
  - The 510(k) Working Group recommends that CDRH develop guidance defining a subset of class II devices, called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would *typically* be necessary to support a substantial equivalence determination. Delineating between "class IIa" and "class IIb" would not reconfigure the current, three-tiered device classification system established by statute; it would represent only an administrative distinction. The development of a "class IIb" guidance would provide greater clarity regarding what submitters would generally be expected to provide for certain 510(k)s. Determining what device types might be included in "class IIb" would require further consideration. Potential candidates may include some implantable, life-sustaining devices, and/or life-supporting devices, which present greater risks than other class II device types. A specific type of device may be removed from the "class IIb" subset as its technology and its risk/benefit profile in clinical practice become better understood. The types of evidence that could be required for "class IIb" devices are discussed in greater detail in the following subsections. As part of its guidance, CDRH should make clear that the delineation between "class IIa" and "class IIb" is meant to be a general guideline only. The types of evidence described below may at times be required for a device that was previously in "class IIa" but for which the Center has changed its evidentiary expectations on the basis of new scientific information, as described in the preliminary report of the Task

Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). In addition, such evidence may be required for a device that has not yet been specifically identified as a "class IIa" or "class IIb" device. For example, in some situations, a new device may be developed whose technology or use may be so new that it is not possible for CDRH to determine whether it should be included in "class IIa" or "class IIb" until it meets with the submitter to obtain more information. Further, it is possible that not all devices within the "class IIb" subset would necessarily require *all* of the types of evidence described below; therefore, the guidance should advise manufacturers of "class IIb" devices to engage with the Center to discuss the type of evidence appropriate for their devices.

- The 510(k) Working Group further recommends that CDRH develop and implement training for review staff and industry regarding the delineation between "class IIa" and "class IIb."

– **Clinical Information**

- The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term "clinical data" to foster a common understanding among review staff and submitters about types of information that may constitute "clinical data." General recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH's mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below). That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.

– **Postmarket Information**

- The 510(k) Working Group recommends that CDRH explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices. If CDRH were to obtain broader authority to require condition-of-clearance studies, the Center should develop guidance identifying the circumstances under which such studies might be appropriate, and should include a discussion of such studies as part of its "class IIb" guidance.
- The 510(k) Working Group further recommends that CDRH continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using "real-world" data (*e.g.*, anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s.

– **Manufacturing Process Information**

- The 510(k) Working Group recommends that CDRH develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its "class IIb" guidance.

- The 510(k) Working Group further recommends that CDRH clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing requirements in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health, and include a discussion of pre-clearance inspections as part of its "class IIb" guidance.

- ***Incorporation of New Information into 510(k) Decision Making***
  - This issue is discussed more fully in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below).

» **Finding:** Limitations in CDRH's information technology (IT) and knowledge management infrastructure and tools make it challenging for Center staff and 510(k) submitters to access meaningful medical device information that would support better-informed and more predictable decision making.

Recommendation: CDRH should take steps to enhance its internal and public information systems and databases to provide easier access to more complete information about 510(k) devices and previous clearance decisions.

- ***Product Codes***
  - The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.
  - The 510(k) Working Group further recommends that CDRH enhance existing staff training on the development and assignment of product codes.

- ***510(k) Databases***
  - **Limited Tools for Review Staff and Outside Parties**
    - The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.
    - The 510(k) Working Group further recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.
  - **Lack of Ready Access to Final Device Labeling**
    - The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for the submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after

clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center's public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance. In exploring this approach, CDRH should consider options to assure that labeling could be screened efficiently, without placing a significant additional burden on review staff. For example, to allow for more rapid review of labeling changes, the Center could consider the feasibility of requiring manufacturers to submit a clean copy and a redlined copy of final labeling and subsequent updates, highlighting any revisions made since the previous iteration. As a longer-term effort, the Center could explore greater use of software tools to facilitate rapid screening of labeling changes. The Center should consider phasing in this requirement, potentially starting with only a subset of devices, such as the "class IIb" device subset described above, or with a particular section of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.

- **Limited Information on Current 510(k) Ownership**
  - The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.

3. Continuous Quality Assurance

» **Finding:** Variations in the expertise, experience, and training of reviewers and managers, including third-party reviewers, may contribute to inconsistency or uncertainty in 510(k) decision making.

Recommendation: CDRH should enhance training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high-quality 510(k) reviews.

- ***Reviewer Expertise and Experience***
  - The 510(k) Working Group recommends that CDRH continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts, as discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making (described further in Section 2, below).
  - The 510(k) Working Group further recommends that CDRH consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. The Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to

improve internal communication and integration. The Science Council's role in improving the consistency of Center decisions is discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.

- ***Third-Party Review***
  - The 510(k) Working Group recommends that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. The Center should consider, for example, limiting eligibility to those device types for which device-specific guidance exists, or making ineligible selected device types with a history of design-related problems.
  - The 510(k) Working Group further recommends that CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.

» **Finding:** CDRH does not currently have an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program.

Recommendation: CDRH should enhance its systems and program metrics to support continuous quality assurance.

- The 510(k) Working Group recommends that CDRH develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.
- The 510(k) Working Group further recommends that CDRH periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency. The ongoing implementation of iReview (described in Section 5.3.2 of this report), as part of the Center's FY 2010 Strategic Priorities, could assist with this effort by allowing CDRH to more efficiently search and analyze completed reviews. These audits should be overseen by the new Center Science Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action.

2. BACKGROUND AND GOALS

The 510(k) medical device review process was established in 1976, under the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA). With the exception of certain low-risk devices that are exempt from premarket submission requirements, a medical device that is first introduced into the market after May 28, 1976 (a postamendment device) may be legally marketed without an approved premarket approval application (PMA) if FDA concludes through review of a 510(k) submission that the device meets the comparative standard of "substantial equivalence" to a "predicate" device. By regulation, substantial equivalence may be determined by a comparison to a device that was legally marketed prior to May 28, 1976 (a preamendment device), to a device that has been reclassified from class III (high-risk) to class II or class I (medium- to low-risk), or to a device that has previously been cleared through the 510(k) process.[4]

Since its inception, the 510(k) process has undergone a number of statutory changes. In addition, FDA has modified its implementation of the process to adapt to changing circumstances and to accommodate the evolving medical device landscape. The current 510(k) program reflects the current statutory framework and FDA's implementation of that framework through regulation, guidance, and administrative practice.[5]

The 510(k) program, as it currently exists, is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that are safe and effective, and fostering innovation in the medical device industry. In recent years, concerns have been raised both within and outside of FDA about whether the current 510(k) program optimally achieves these goals.[6] Some have asserted that the program needs to be fundamentally re-thought — that a determination of substantial equivalence to a predicate is insufficient to provide reasonable assurance that marketed devices are safe and effective. Others have argued that the statutory and regulatory framework of the program is sound, but that a lack of transparency and consistency in the way the program is currently administered may be hindering innovation.

In light of these concerns, and in keeping with the good government practice of periodically assessing the effectiveness of existing programs, CDRH launched in September 2009 a two-pronged, comprehensive assessment of the 510(k) process to determine whether changes should be made to the program so that it can better achieve its goals. One part of this assessment is an ongoing independent evaluation by the Institute of Medicine (IOM), which is expected to conclude in the summer of 2011.[7] In addition to this external review, CDRH convened an internal 510(k) Working Group to evaluate the

[4] *See* Section 4 of this report for an overview of medical device regulation, including references to relevant statutory provisions and FDA regulations.

[5] *See* Section 4 of this report for a discussion of the 510(k) program's inception and evolution, including major legislative, regulatory, and administrative milestones.

[6] *See, e.g.,* U.S. House, Committee on Energy and Commerce, Subcommittee on Health, "Medical Devices: Are Current Regulations Doing Enough for Patients?" Hearing (June 18, 2009). Available at http://energycommerce.house.gov/index.php?option=com_content&view=article&id=1677:energy-and-commerce-subcommittee-hearing-on-medical-devices&catid=132:subcommittee-on-health&Itemid=72. *See also* U.S. Food and Drug Administration, "Review of the ReGen Menaflex: Departures from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question, Preliminary Report" (September 2009). Available at http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM183642.pdf.

[7] *See* Institute of Medicine, "Public Health Effectiveness of the 510(k) Clearance Process." Available at http://www.iom.edu/Activities/PublicHealth/510KProcess.aspx.

510(k) process and explore actions the Center could take to strengthen the program and increase the consistency of its premarket decision making. While the Working Group focused primarily on actions the Center could take in the short term under its existing authority, it also considered potential longer-term changes.

The goal of the Working Group was to identify ways CDRH could improve the 510(k) program so that it can more effectively support FDA's mission to protect and promote the public health, both providing confidence that cleared devices have a reasonable assurance of safety and effectiveness, and providing a predictable regulatory pathway that fosters innovation.

Other ongoing initiatives at CDRH were or are aimed, at least in part, toward similar goals. The Task Force on the Utilization of Science in Regulatory Decision Making, for example, was convened in September 2009 to review how CDRH uses science in its regulatory decision making processes and to make recommendations on how the Center can quickly incorporate new science —including evolving information, novel technologies, and new scientific methods — into its decision making, while also maintaining as much predictability as practical.[8] The 510(k) Working Group decided that where its efforts touched on an issue that was being addressed by another more cross-cutting group, as in the case of the Task Force on the Utilization of Science in Regulatory Decision Making or any other project listed as part of the Center's FY 2010 Strategic Priorities,[9] it would defer to that group. At various points in this report, therefore, the Working Group refers to such projects.

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[8] *See* "CDRH Preliminary Internal Evaluations – Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations." Available at http://www.fda.gov/FDAgov/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220272.

[9] "CDRH FY 2010 Strategic Priorities." Available at http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHVisionandMission/ucm197647.htm.

3. WORKING GROUP METHODS

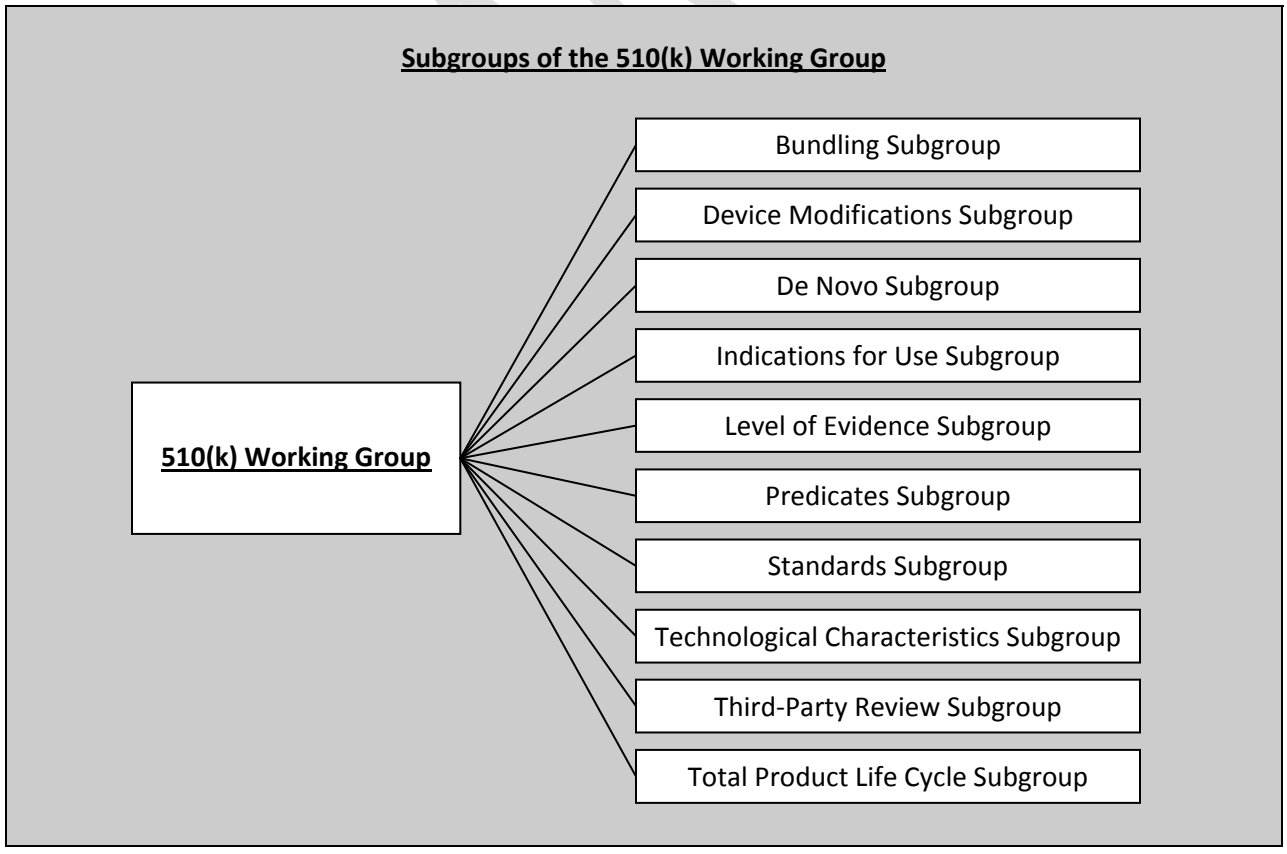
In an effort to develop as rich an understanding as possible of the way the 510(k) process currently functions, the perspectives of CDRH staff and a range of external constituencies on the program, and potential areas for improvement, the 510(k) Working Group gathered input and information from a variety of sources both within and outside of the Center.

3.1. Working Group Structure

As a Center-wide initiative, the 510(k) Working Group was comprised of representatives from across CDRH. In order to better accommodate the breadth of its charge and to allow for a significant level of staff participation, the Working Group developed 10 subgroups, each of which was assigned a specific area of focus within the broader 510(k) framework. The primary topics considered by these subgroups are illustrated in the box below.

To capture a range of perspectives on and experiences with the 510(k) program, each subgroup was made up of CDRH staff at various organizational levels. Under the direction of a designated chairperson, each subgroup met regularly, discussed relevant information and data from multiple sources (described in greater detail below), and developed findings and recommendations related to its assigned topic. Subgroup chairs met on a regular basis to discuss their progress and identify cross-cutting issues.

In addition to these content-specific subgroups, the Working Group convened a team of staff to pool and analyze quantitative data from a variety of sources within the Center (see Section 3.4).



3.2. Staff Participation

In order to collect additional input from Center staff, the Working Group co-hosted a staff-wide internal town hall meeting on February 24, 2010, in conjunction with the Task Force on the Utilization of Science in Regulatory Decision Making. The Working Group also encouraged Center staff to provide written comments on its ongoing work through email and through a web-based social media tool.[10]

3.3. Public Participation

To gather input from CDRH's external constituencies, the Working Group held a public meeting on February 18, 2010.[11] The group also collected written comments through a public docket that was open from January 27, 2010 through March 19, 2010.[12]

3.4. Other Sources of Information

In an effort to maintain objectivity in its review, the 510(k) Working Group collected and analyzed relevant quantitative data from a variety of sources within the Center. Summaries of these analyses are provided throughout this report.

3.4.1. Reviewer Survey

To assess the consistency of CDRH reviewers' interpretation and understanding of 510(k) regulations, guidance documents, and review practices, the Working Group conducted a survey of the Center's premarket reviewers and managers.[13] The survey consisted of twenty questions related to reviewers' and managers' knowledge and opinions on a range of identified areas of concern, including many of the Subgroup topics listed above.

Reviewer Cohort. The survey was sent by email to all reviewers in CDRH's two premarket review offices, the Office of Device Evaluation (ODE) and the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD). All reviewers were strongly encouraged to complete it. Out of a total of 308 reviewers, 215 reviewers took the survey, and at least 162 respondents answered each question.

Manager Cohort. Premarket review managers also completed the survey as a separate cohort of respondents. Out of a total of 38 managers (Branch Chiefs, Deputy Division Directors, and Division Directors) in ODE and OIVD, 21 ODE Branch Chiefs and Deputy Division Directors took the survey, and at least 13 respondents answered each question.

3.4.2. CDRH Databases

CDRH's internal databases and electronic records systems contain a significant amount of information about the roughly 4,000 510(k) submissions the Center reviews each year. CDRH also collects postmarket data on cleared devices, such as adverse event reports, inspection results, and recall information. The 510(k) Working Group pooled premarket and postmarket data from all relevant internal databases and analyzed it to identify any apparent trends or correlations. This is the first time such an analysis has been conducted.

[10] *See* Appendix A for a summary of staff feedback.
[11] *See* Appendix B for summary of the public meeting.
[12] *See* Appendix C for a summary of written public comments.
[13] *See* Appendix D for a full listing of the Reviewer Survey questions and results.

The Working Group extracted data on all 510(k)s reviewed between January 1, 2005 and December 31, 2009 (N=18,332). The group identified over one hundred measurable 510(k) characteristics, including submission type and related submissions, and analyzed the relationship between these variables and various outcomes, including review decision and related adverse events. In some cases, extracted data were used to derive data elements of interest, such as years of reviewer experience (*i.e.*, time from receipt of the reviewer's first 510(k) to receipt of a given 510(k)) and predicate age (*i.e.*, time from predicate clearance to receipt of a given 510(k)).

Limitations. CDRH's information technology (IT) systems and data sources have several recognized limitations. For example, some data fields are inconsistently entered into the Center's data systems, leading to inaccuracies and missing data. In addition, due to limitations in postmarket reporting, it is not always possible to accurately link postmarket information, such as specific adverse event reports and recalls, to a particular 510(k) submission. Further, CDRH does not have ready access to meaningful "denominator data" (*i.e.*, the number of units of a particular device in use during the relevant time period) that could provide insight into the relative rates of reported adverse events and recalls. It is also difficult to decipher, in the case of adverse event reporting, the impact of varied reporting dynamics (*e.g.*, reporting practices and reporting biases) on the findings. If the reporting rates are not independent of other factors included in an analysis, then any observed trends may be misleading.

In addition, any novel analysis has potential shortcomings. Given that there were so many potentially related variables in the Working Group's dataset, there may be confounding factors that the Working Group did not consider. Although the Working Group identified correlations between certain 510(k) characteristics and outcomes, causal relationships remain unclear. Further exploratory analyses would need to be conducted to better understand potential associations.

Further detail regarding the definitions of and limitations associated with specific data elements is provided in footnotes throughout this report.

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4. HISTORY OF THE 510(K) PROGRAM

The 510(k) program was established under the Medical Device Amendments of 1976. Since that time, the program has been periodically modified by statute, regulation, or FDA practice to adapt to changing circumstances and to accommodate the evolving medical device landscape.

4.1. Overview of Medical Device Regulation

In keeping with FDA's mission to protect and promote the public health, CDRH is responsible for assuring that medical devices marketed in the United States provide a reasonable assurance of safety and effectiveness.[14]

With the passage of the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA),[15] Congress provided FDA with the authority to regulate medical devices. However, Congress initially limited FDA's authority with respect to devices to postmarket adulteration and misbranding provisions. Over the next four decades, FDA regulated device manufacturers by prosecuting those who misbranded or adulterated their devices.

Congress expanded FDA's authority over medical devices with the enactment of the Medical Device Amendments of 1976 (MDA).[16] The MDA provided FDA with the regulatory framework that applies to medical devices today. In identifying a regulatory scheme, Congress was concerned with establishing a mechanism that affords the public with a reasonable assurance that medical devices are safe and effective and providing FDA with the authority to remove dangerous devices from the marketplace, while balancing the need for innovative development of new and improved devices.[17] To address this concern, the MDA established a three-tiered regulatory system with safety and effectiveness requirements applicable to all medical devices, and a classification scheme requiring that devices be placed into one of three groups: class I, class II, or class III. Generally, the classification of a device is determined based on the risk associated with the device and the level of regulatory control necessary to provide reasonable assurance of safety and effectiveness.

The three medical device classes established by the MDA are as follows:

- **Class I**: Devices for which the general controls[18] of the FDCA are sufficient to provide reasonable assurance of safety and effectiveness.

[14] Under 21 CFR 860.7(d)(1), there is a *reasonable assurance of safety "*when it can be determined, based upon valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks." Under 21 860.7(e)(1), there is a *reasonable assurance of effectiveness* "when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

[15] Pub. L. No. 75-717, 52 Stat. 1040 (1938).

[16] The Medical Device Amendments were enacted on May 28, 1976. *See* Pub. L. No. 94-295, 90 Stat. 539.

[17] *See* H.R. Rep. No. 11124, 94th Cong. 2d Sess. (1976), at 12.

[18] General controls apply to all classes of medical devices and provide FDA with the means of regulating devices to assure their safety and effectiveness. General controls include but are not limited to provisions that relate to establishment registration and device listing; premarket notification; notification including repair, replacement, or refund; records and reports; and good manufacturing practices.

- **Class II**: Devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance.[19]
- **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.

In the years following the enactment of the MDA, FDA classified nearly all device types[20] introduced or delivered for introduction into interstate commerce before the date of enactment of the MDA (otherwise known as preamendment devices) into one of these three regulatory classes. A device that was not on the market prior to enactment of the MDA (otherwise known as a postamendment device) may be classified through FDA's review of a premarket notification for the device, and it is placed into one of the three classes based on FDA's determination of whether the device is "substantially equivalent" to a predicate device. A premarket notification is also called a "510(k) submission" or "510(k)," after the section of the FDCA that describes the notification requirement. Devices found not substantially equivalent to a predicate device are automatically placed into class III.[21]

In general, unless exempt under FDA regulations,[22] medical devices are subject to one of two types of FDA premarket review which are intended, in conjunction with general and special controls, as applicable, to provide reasonable assurance of safety and effectiveness:[23]

- **Premarket notification (510(k)):** The submitter must demonstrate that the new device is substantially equivalent to a device already legally on the market that does not require a premarket approval application (PMA).[24]
- **Premarket approval:** The submitter must independently demonstrate reasonable assurance of the safety and effectiveness of the new device for its intended use.

The premarket notification process is intended to provide a mechanism for the classification of a device that is found to be substantially equivalent to a predicate device not subject to premarket approval.

[19] The original definition of a class II device identified performance standards rather than special controls as the mechanism by which FDA could establish reasonable assurance of the safety and effectiveness. The Safe Medical Devices Act of 1990 added "special controls," which can include the promulgation of performance standards as well as postmarket surveillance, patient registries, development and dissemination of guidance documents, and other appropriate actions as FDA deems necessary to provide such assurance.

[20] The terms "type of device" and "device type" are used throughout this report to indicate a generic category of device, which has a particular intended use and which may include a variety of devices made by different manufacturers. *See* 21 CFR 860.3(i) for the regulatory definition of "generic type of device." FDA's classifications of device types are codified in Title 21 Code of Federal Regulations Parts 862 through 892.

[21] Section 513(f) of the FDCA (21 USC §360c(f)) identifies the classification procedures for medical devices.

[22] Some class I and class II devices have been exempted from the premarket notification requirement by statute and/or regulation.

[23] A small percentage of devices enter the market by other means, such as through the humanitarian device exemption process that allows market entry, without adherence to certain requirements, for devices benefiting patients with rare diseases or conditions. *See* section 520(m) of the FDCA (21 USC §360j(m)); 21 CFR Part 814, subpart H.

[24] Generally, a device that does not require a PMA is one for which there is a reasonable assurance of safety and effectiveness with general and special controls, as applicable.

Generally, premarket approval is required for class III devices[25] and is used for reviewing the safety and effectiveness of such devices.

4.2. Interpreting and Implementing Section 510(k) of the FDCA

The MDA established the premarket notification requirement by adding section 510(k) to the FDCA.

Section 510(k) of the FDCA [26]

Each person who is required to register under this section and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to [FDA]…

(1) the class in which the device is classified under section 513 or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified, and

(2) action taken by such person to comply with requirements under section 514 or 515 which are applicable to the device.

The statutory language of section 510(k) of the FDCA can be viewed as requiring three actions of manufacturers.[27] First, a manufacturer must notify FDA at least 90 days prior to marketing a new device. Second, the manufacturer must provide the class in which the device is classified or a statement that it is not so classified and the basis for that determination. Finally, the manufacturer must identify the actions it has taken to comply with the applicable performance standard or premarket approval requirements under sections 514 and 515 of the FDCA,[28] respectively. The statutory language of section 510(k) does not contain any affirmative requirements as to how FDA should review premarket notifications.

The MDA also added section 513(f)(1) to the FDCA,[29] which includes requirements for initial device classification and introduced the term "substantially equivalent." Later revisions to the FDCA defined this term, as described in Section 4.3.1, below.

Section 513(f)(1) of the FDCA [30]

Any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before the date of enactment of this section is

[25] Certain types of devices classified into class III that were in commercial distribution in the United States before May 28, 1976, and those determined to be substantially equivalent to such devices, may be cleared through the 510(k) process until FDA publishes regulations requiring them to go through the PMA process or reclassifies them into a lower class.

[26] 21 USC §360.

[27] For the sake of ease, this section refers to obligations of "manufacturers." Note, however, that these obligations apply not only to manufacturers, but to any "owner or operator" of an establishment engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of medical devices. *See* 21 CFR 807.20(a). "Owner or operator" is defined as "the corporation, subsidiary, affiliated company, partnership, or proprietor directly responsible for the activities of the registering establishment." 21 CFR 807.3(f).

[28] 21 USC §360d and 21 USC §360e, respectively.

[29] 21 USC §360.

> classified in class III unless —
>
> (A) the device —
>
> (i) is within a type of device (I) which was introduced or delivered for introduction into interstate commerce for commercial distribution before such date and which is to be classified pursuant to subsection (b), or (II) which was not so introduced or delivered before such date and has been classified in class I or II, and
>
> (ii) is *substantially equivalent* to another device within such type….

After the passage of the MDA, FDA issued implementing regulations for the premarket notification process. On August 23, 1977, FDA issued a final rule describing premarket notification procedures.[31] The regulations describe the circumstances under which a 510(k) must be submitted, the information required, and the FDA rules for maintaining confidentiality of submitted information. Essentially, the regulations provide that a person required to register must submit a 510(k) at least ninety days before marketing a device that: (1) is being introduced into commercial distribution for the first time by that person, or (2) is in commercial distribution but is being significantly changed or modified in design, components, method of manufacture, or intended use.[32] The regulations also make it clear that FDA will actively make determinations of substantial equivalence as part of the premarket notification process.[33]

4.2.1. Developing a "Substantial Equivalence" Policy

FDA looked to the legislative history for guidance on how to interpret and apply the statutory standard established by the MDA. The House Report stated:

> 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 so 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.[34]

Based on the statutory language and the legislative history, in 1986 CDRH developed its "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)" (*hereinafter* K86-3 or the 1986

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[30] 21 USC §360c(f)(1), emphasis added.

[31] 42 Fed. Reg. 42520 (Aug. 23, 1977). FDA issued a final regulation entitled *Establishment Registration and Premarket Notification Procedures* (21 CFR Part 807). Subpart E describes premarket notification procedures. The 510(k) rules were incorporated into the registration and listing regulation because the 510(k) requirements apply only to those persons required to register.

[32] 21 CFR 807.81(a)(3).

[33] 21 CFR 807.92(a)(3) and 807.100. Regulations identifying premarket notification procedures can be found at 21 CFR 807 Subpart E.

[34] H.R. Rep. No. 94-853 (1976), at 36-37.

guidance), identifying points CDRH would consider when making a determination that a device is or is not substantially equivalent to a predicate. The document was FDA's first formal articulation of the purpose of the 510(k) program and of the review standard.

K86-3 asserted that if substantial equivalence were judged too narrowly: (1) the marketing of devices that would benefit the public would be delayed; (2) the device industry would be unnecessarily exposed to the greater burdens of premarket approval; (3) new devices would not be properly classified; and (4) new manufacturers of preamendment type devices would not have marketing equity. If substantial equivalence were judged too broadly, however, the statutory purpose may not be served, *i.e.*, devices with new uses or those presenting new or different risks would be marketed without adequate regulatory control. K86-3 also identified a series of questions and a corresponding flowchart that was intended to guide reviewers in making substantial equivalence decisions. The flowchart, which is still in use today, is provided on page 27 of this report.

K86-3 identified the following points CDRH would consider when making a substantial equivalence decision:

- Does the new device have the same intended use as a predicate device?
- Does the new device have the same technological characteristics, *i.e.*, same materials, design, energy source, etc.?
- If it has new technological characteristics, could they affect safety or effectiveness?[35]

If the new device has a new intended use, it is considered not substantially equivalent (NSE). If the new device has the same intended use as a predicate device and the same technological characteristics related to safety and effectiveness, or new technological characteristics but those new characteristics could not affect safety or effectiveness, the new device may be considered substantially equivalent (SE). However, if the new device has the same intended use as a predicate device, but it has new technological features that could affect safety or effectiveness, CDRH considers additional issues such as:

- Do the new technological features pose the same type of questions about safety or effectiveness as are posed by the predicate device with the same intended use?
- Are there accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics?
- Is there information to demonstrate that the new technological features have not diminished safety and effectiveness?

If the answers to any of the above questions are negative, the device is generally considered NSE.

Thus, K86-3 indicates that, as a matter of practice, CDRH generally considers a device to be SE to a predicate device if, in comparison to the predicate device:

- The new device has the same intended use; and,

[35] "Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program 6/30/86 (K86-3)" (June 30, 1986), at 2. Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm.

- The new device has the same technological characteristics, (*i.e.*, same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or effectiveness; or
- It has new technological characteristics that could affect safety or effectiveness, and
    - There are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and
    - There are data to demonstrate that the new technological features have not diminished safety or effectiveness.

In addition to establishing a framework for making substantial equivalence determinations, K86-3 also provided guidelines for decision making with respect to intended use and technological characteristics. The framework and guidelines are still used by CDRH today.

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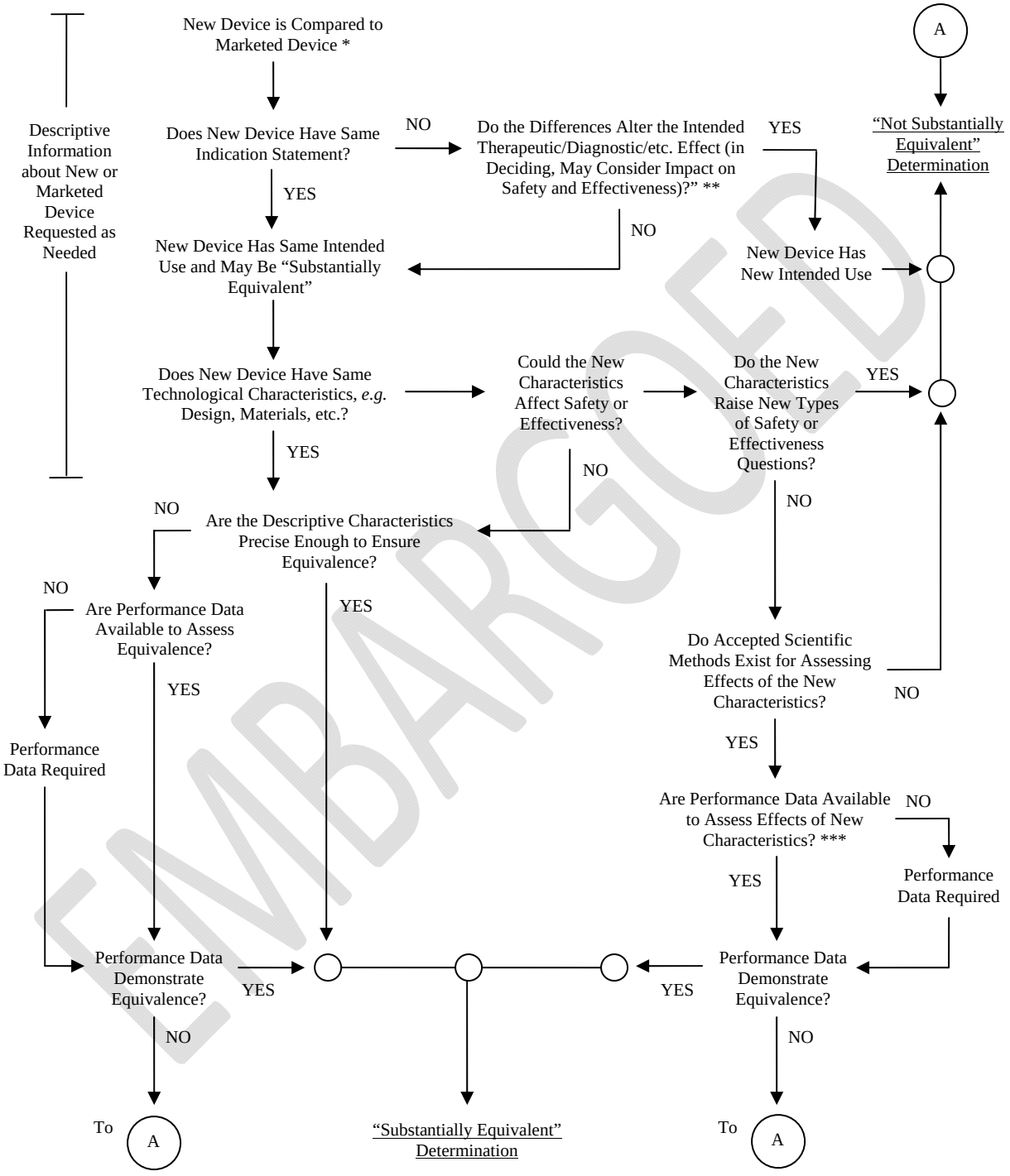
510(K) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data may be in the 510(k), other 510(k)s, the Center's classification files, or the literature.

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4.3. Changes to the 510(k) Program

Since the passage of the Medical Device Amendments, Congress has periodically revised and updated FDA's authority over medical devices through amendments to the FDCA. Many of these amendments have directly affected the premarket notification program.

4.3.1. Safe Medical Devices Act of 1990 (SMDA)

The Safe Medical Devices Act of 1990[36] revised FDA's device authority.

4.3.1.1. Statutory Definition of Substantial Equivalence

SMDA provided a statutory definition for "substantial equivalence," incorporating key elements from FDA's previous interpretation of that term as articulated in K86-3. SMDA also included the term "predicate" and established class III certifications, as well as 510(k) summaries and statements. Where FDA previously relied on legislative history and guidance, the SMDA gave FDA express statutory language to support the 510(k) decision-making process.

Section 513(i)(1)(A) of the FDCA [37]

For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term "substantially equivalent" or "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 as the predicate device, or

(ii) (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by [FDA] or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

4.3.1.2. Special Controls

SMDA revised the original classification criteria for class II devices. The MDA identified performance standards as the mechanism by which FDA could establish reasonable assurance of the safety and effectiveness of certain devices. SMDA included "special controls," which can include the promulgation of performance standards as well as postmarket surveillance, patient registries, development and dissemination of guidance documents, and other appropriate actions as FDA deems necessary to provide such assurance. This authority gave FDA more flexibility in identifying the controls necessary to provide reasonable assurance of the safety and effectiveness of class II devices.

4.3.1.3. Postmarket Surveillance

SMDA added section 522, Postmarket Surveillance, to the FDCA.[38] As amended by Food and Drug Administration Modernization Act of 1997 (FDAMA)[39] and the Food and Drug Administration

[36] Pub. L. No. 101-629, 104 Stat. 4511.
[37] 21 USC §360c(i)(1)(A).
[38] 21 USC §360l.

Amendments Act of 2007 (FDAAA),[40] this section provides FDA with the authority to "require a manufacturer to conduct postmarket surveillance for any device of the manufacturer that is a class II or class III device — (i) the failure of which would be reasonably likely to have serious adverse health consequences; (ii) that is expected to have significant use in pediatric populations; or that is intended to be — (I) implanted in the human body for more than 1 year, or (II) a life sustaining or life supporting device used outside a device user facility." Generally, FDA may require postmarket surveillance studies for a period of up to 36 months; however, a longer study period may be established under certain circumstances.[41]

Postmarket issues may be identified through a variety of sources, including analysis of adverse event reports, a recall or corrective action, reports from other governmental authorities, or the scientific literature.

4.3.2. Food and Drug Administration Modernization Act of 1997 (FDAMA)

The Food and Drug Administration Modernization Act of 1997[42] included provisions that: (1) specifically exempted from the premarket notification requirement most class I devices and those types of class II devices identified by FDA; (2) codified the third-party premarket notification review program, which was based on an FDA pilot; (3) allowed for the classification of low-risk devices automatically classified into class III because they were found not substantially equivalent due to lack of a predicate device (Evaluation of Automatic Class III Designation or the de novo classification process); (4) required FDA to consider the least burdensome means of demonstrating device effectiveness and substantial equivalence; and (5) permitted FDA to require a statement in device labeling to indicate risks of off-label use of a 510(k) device if FDA finds a "reasonable likelihood" of such off-label use and that such use could cause harm.

4.3.2.1. Exemption of Class I and Some Class II Devices

In an effort to manage FDA's workload and allocate resources most appropriately, prior to FDAMA the agency had exempted some class I devices for which it determined that the premarket notification requirements were not necessary to provide reasonable assurance of safety and effectiveness. FDAMA included a provision to exempt class I devices from premarket notification, unless the device is intended for a use that is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury.[43]

FDAMA also included a provision to exempt from premarket notification certain class II devices identified by FDA.[44] FDA published a list of such devices, as required by section 510(m) of the FDCA,[45] and has periodically updated this list over time.[46] FDA may continue to exempt class II devices from the premarket notification requirements by order, when FDA determines that a premarket notification for the class II device is not necessary to assure the safety and effectiveness of the device. In making this determination, FDA considers the following factors: (1) the device does not have a significant history of

[39] Pub. L. No. 105-115, 111 Stat. 2296.
[40] Pub. L. No. 110-85, 121 Stat. 823.
[41] Section 522(b) of the FDCA (21 USC §360l(b)).
[42] Pub. L. No. 105-115, 111 Stat. 2296.
[43] Section 510(l) of the FDCA (21 USC §360(l)).
[44] Section 510(m) of the FDCA (21 USC §360(m)).
[45] 21 USC §360(m).
[46] FDA maintains a list of 510(k)-exempt devices at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm.

false or misleading claims or of risks associated with inherent characteristics of the device, such as device design or materials; (2) characteristics of the device necessary for its safe and effective performance are well-established; (3) changes in the device that could affect safety or effectiveness will either: (a) be readily detectable by users by visual examination or other means such as routine testing, before causing harm, *e.g.*, testing of a clinical laboratory reagent with positive and negative controls; or (b) not materially increase the risk of injury, incorrect diagnosis, or ineffective treatment; and (4) any changes to the device would not be likely to result in a change in the device's classification.[47] FDA considers that, even when it exempts certain devices, such devices are still subject to the limitations on exemptions that FDA has established by regulation.[48]

4.3.2.2. Third-Party Review

FDAMA included a provision on the accreditation of third parties to help improve the efficiency and timeliness of FDA's 510(k) review process.[49] Under the program, FDA has accredited third parties (accredited persons) to conduct the primary review of 510(k)s for eligible devices.[50] Persons required to submit 510(k)s for these devices may elect to contract with an Accredited Person and submit a 510(k) directly to the Accredited Person for review. The Accredited Person conducts the primary review of the 510(k), then forwards its review, recommendation, and the 510(k) to FDA for the final decision.

4.3.2.3. Evaluation of Automatic Class III Designation (De Novo Classification) Process

FDAMA amended section 513(f)(2) of the FDCA[51] to provide a mechanism for classifying new devices for which there is no predicate device. The de novo classification process is intended to apply to lower-risk devices that are classified into class III through the 510(k) process. The de novo process is generally used where the risks of the device are well-understood and appropriate special controls can be established to mitigate those risks.

A 510(k) submitter who receives an NSE determination may request a de novo classification of the device into class I or II. The request must be in writing and sent within 30 days from the receipt of the NSE determination.[52] The de novo process has a 60-day review period. If FDA classifies the device into class I or II, the petitioner will then receive a written order classifying the device. This device may then be used as a predicate for future 510(k)s. However, if FDA determines that the device will remain in class III, the device may not be marketed until the applicant has obtained an approved PMA.

4.3.2.4. Least Burdensome Provisions

One of the goals of FDAMA was "to ensure the timely availability of safe and effective new products that will benefit the public…."[53] To help achieve this goal, Congress added sections 513(a)(3)(D)(ii) and 513(i)(1)(D) to the FDCA.[54] These provisions, known as the "least burdensome provisions," require FDA

[47] *See* 63 Fed. Reg. 3142, 3143 (Jan. 21, 1998).

[48] *See* "Medical Device Exemptions 510(k) and GMP Requirements," available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm; *see also*, *e.g.*, 21 CFR 862.9.

[49] Section 523 of the FDCA (21 USC §360m).

[50] FDA maintains a list of devices eligible for third-party review at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfThirdParty/current.cfm.

[51] 21 USC §360c(f)(2).

[52] Section 513(f)(2) of the FDCA (21 USC §360c(f)(2)).

[53] S. Rep. No. 105-43, 105th Cong., 1st Sess. (1997), at 2.

[54] 21 USC §360c(a)(3)(D)(iii) and 21 USC §360c(i)(1)(D), respectively.

to limit certain types of requests for data or information in a premarket review to that which is necessary to determine if the device meets the applicable statutory standard for clearance or approval.

The first of these provisions pertains to data needed to determine device effectiveness in PMAs. It states:

> Any clinical data, including one or more well-controlled investigations, specified in writing by [FDA] for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by [FDA] that such data are necessary to establish device effectiveness. [FDA] shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.[55]

The second provision pertains specifically to substantial equivalence determinations when the new device has different technological characteristics than the predicate device that do not raise different questions of safety or effectiveness:

> Whenever [FDA] requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, [FDA] shall only request information that is necessary to making substantial equivalence determinations. In making such requests, [FDA] shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.[56]

In response to these provisions, FDA issued in 2002 "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry."[57,58]

4.3.2.5. Substantial Equivalence with Limitations

FDAMA included a new section 513(i)(E) of the FDCA.[59] This provision states that, in determining the intended use of a device, "any determination by [FDA] of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k)."[60] However, this section also provides authority to FDA to require "a statement in device labeling that provides appropriate information regarding the use of a device not identified in the proposed labeling," if FDA determines that there is a "reasonable likelihood" that the device will be used for an intended use not identified in the proposed labeling for the device, and that such use could cause harm.[61]

[55] Section 513(a)(3)(D)(ii) of the FDCA (21 USC §360c(a)(3)(D)(ii)).

[56] Section 513(i)(1)(D) of the FDCA (21 USC §360c(i)(1)(D)).

[57] "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry" (October 4, 2002). Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085999.pdf.

[58] The least burdensome provisions are discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.

[59] 21 USC §360c(i)(E).

[60] Section 513(i)(1)(E) of the FDCA (21 USC §360c(i)(1)(E)).

[61] *Id*.

In 2002, FDA issued "Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1)," which describes agency procedures for issuing so-called "SE with limitations" letters, consistent with the new section 513(i)(E).[62]

4.3.3. The New 510(k) Paradigm

In 1998, FDA issued a guidance document entitled "The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications."[63] This guidance provided recommendations related to two new optional approaches for 510(k) submitters. While the New 510(k) Paradigm maintained the traditional method of demonstrating substantial equivalence under section 510(k) of the FDCA, it also introduced the "Special 510(k): Device Modification" option, which utilizes certain aspects of the Quality System Regulation, and the "Abbreviated 510(k)" option, which relies on the use of guidance documents, special controls, and recognized consensus standards to demonstrate substantial equivalence.[64]

These two options still exist today. FDA may convert either a Special 510(k) or an Abbreviated 510(k) into a traditional 510(k) if it finds that the submission contains modifications that may affect the intended use or alter the fundamental scientific technology of the device.

4.3.3.1. Special 510(k): Device Modification

FDA's regulations implementing section 510(k) of the FDCA require the submission of a new 510(k) when a manufacturer makes certain modifications to its device.[65] Further, the Quality System (QS) regulations require class II and III devices and certain class I devices be designed in conformance with design controls.[66]

According to FDA's guidance on the New 510(k) Paradigm, the "Special 510(k): Device Modification" utilizes the design control requirement of the Quality System Regulation and may be submitted for a modification to a 510(k) holder's own cleared device, as long as the modification does not affect the intended use of the device or alter its fundamental scientific technology.[67] The Special 510(k) allows a submitter, under certain circumstances, to declare conformity to design controls in lieu of providing detailed performance data to FDA as part of its 510(k).[68] The guidance specifies that, in addition to containing the required elements of a traditional 510(k), Special 510(k)s should also reference the 510(k) number of the previous cleared version of the device and contain a "Declaration of Conformity" with design control requirements.[69]

[62] "Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1)" (December 3, 2002). Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082166.pdf.

[63] "The New 510(k) Paradigm Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications" (March 20, 1998). Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080189.pdf.

[64] *Id.* at 2.

[65] 21 CFR 807.81(a)(3).

[66] 21 CFR Part 820.

[67] "The New 510(k) Paradigm," at 3.

[68] *Id.* at 3-4.

[69] *Id.* at 4.

The guidance states that, when first implemented, in order to provide an incentive for manufacturers to choose this option for review to seek FDA clearance for modifications to a firm's own device, FDA aimed to process Special 510(k)s within 30 days of receipt.[70]

4.3.3.2. Abbreviated 510(k)

According to FDA's guidance on the New 510(k) Paradigm, in the years preceding the development of the New 510(k) Paradigm, FDA had begun to place greater emphasis on the development of guidance documents, special controls, and the recognition of individual consensus standards to communicate regulatory and scientific expectations to industry. When FDA developed the New 510(k) Paradigm, it believed that compliance with device-specific guidance documents, special controls, and consensus standards could be used to address a specific risk or issue and to provide an effective means of streamlining the review of 510(k)s through a reliance on a "summary report" outlining adherence to relevant documents. At the time, FDA believed that a 510(k) submission that conformed with any of these documents would be easier to prepare and review, thus resulting in a more expeditious evaluation of the 510(k).[71]

The guidance specifies that device manufacturers may choose to submit an Abbreviated 510(k) when: (1) a guidance document exists; (2) a special control has been established; or (3) FDA has recognized a relevant consensus standard. In addition to the required elements of a traditional 510(k), manufacturers submitting an Abbreviated 510(k) elect to provide summary reports on the use of guidance documents and/or special controls, or declarations of conformity to recognized standards.[72]

4.3.4. Medical Device User Fee and Modernization Act of 2002 (MDUFMA)

4.3.4.1. User Fees

The Medical Device User Fee and Modernization Act of 2002[73] amended the FDCA by authorizing FDA to collect user fees for certain premarket submissions received on or after October 1, 2002 to improve the timeliness of premarket review and enhance postmarket safety by increasing FDA staffing and improving FDA infrastructure for these activities. Under MDUFMA, FDA committed to improving its premarket review times by meeting review cycle and decision performance goals for 510(k)s and other premarket submissions.[74]

4.3.4.2. Bundling

"Bundling" refers to the inclusion of multiple devices or multiple indications for use for a device in a single premarket submission (510(k) or PMA). Throughout the history of the 510(k) program, FDA has

[70] *Id.* at 5.
[71] *Id.* at 8.
[72] *Id.* at 9.
[73] Pub. L. No. 107-250, 116 Stat. 1588.
[74] FDA's performance goals for FY 2003 through FY 2007 included the following: "1. The following goals apply to: 70% of submissions received in fiscal year 2005; 80% of submissions received in fiscal year 2006; 90% of submissions received in fiscal year 2007. (a) First action additional information letters will issue within 75 [FDA] days. (b) Subsequent action letters will issue within 60 [FDA] days. 2. Decision Goals: (a) 75% of submissions received in fiscal years 2005 and 2006 will have an FDA decision in 90 [FDA] days. 3. … 80% of submissions received in fiscal year 2007 will have an FDA decision in 90 [FDA] days." *Congressional Record*, 107th Cong., 2d Sess., 2002, 148, No. 150 (November 22, 2002): S11549. Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109138.htm.

accepted submissions in which multiple devices or indications for use are bundled, when the devices or indications present issues that could be addressed through the review of a single submission instead of separate submissions.

Prior to MDUFMA, inappropriate bundling (*i.e.*, submitting separate submissions for devices that could have been bundled in a single submission, or bundling devices that should have been submitted in separate submissions) was largely an administrative problem whose impact primarily related to the efficiency of the review process. However, bundling took on additional importance after the introduction of user fees and review performance goals. If multiple devices or multiple indications for use are bundled in a single premarket submission when they should have been submitted in separate submissions, user fee revenues are affected. In addition, if multiple devices or multiple indications for use are bundled inappropriately, it may be more challenging to meet performance goals. In light of these concerns, FDA issued guidance on appropriate bundling soon after the implementation of MDUFMA.[75]

4.3.5. Medical Device User Fee Amendments of 2007 (MDUFA)

The Medical Device User Fee Amendments of 2007 (Title II of the Food and Drug Administration Amendments Act of 2007 (FDAAA))[76] reauthorized the user fee program and extended the third-party review program. After the passage of MDUFA, FDA eliminated its 510(k) review cycle goals and committed to more challenging 510(k) decision goals than those established under MDUFMA.[77]

4.4. The Current 510(k) Program

As described above, the 510(k) program has changed significantly since its inception. The MDA established the premarket notification process as a simple check to assure proper device classification. Through various statutory and regulatory modifications over time, it has become a multifaceted premarket review process that is expected to assure that cleared devices, subject to general and applicable special controls, provide reasonable assurance of safety and effectiveness, and to facilitate innovation in the medical device industry.

Figures 4.1 and 4.2, below, show the number of 510(k)s CDRH has received each year since 1976, and the annual breakdown of different types of 510(k) submissions since 1998. For the past decade, CDRH has received a total of roughly 4,000 original 510(k)s each year — the largest number of annual submissions of any premarket review program at FDA.

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[75] *See* "Guidance for Industry and FDA Staff: Bundling Multiple Devices or Multiple Indications in a Single Submission" (June 22, 2007), which superseded two related 2003 guidance documents. Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089731.htm.

[76] Pub. L. No. 110-85, 121 Stat. 823.

[77] FDA's performance goals for FY 2008 through FY 2012 include the following: "FDA will issue a decision for 90% 510(k)s within 90 [FDA] days, and for 98% within 150 [FDA] days." Leavitt M, Letter to Senator Edward Kennedy (September 22, 2007). Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/UCM109102.pdf.

Figure 4.1. Original 510(k)s Received by CDRH: FY 1976-2009 [78]

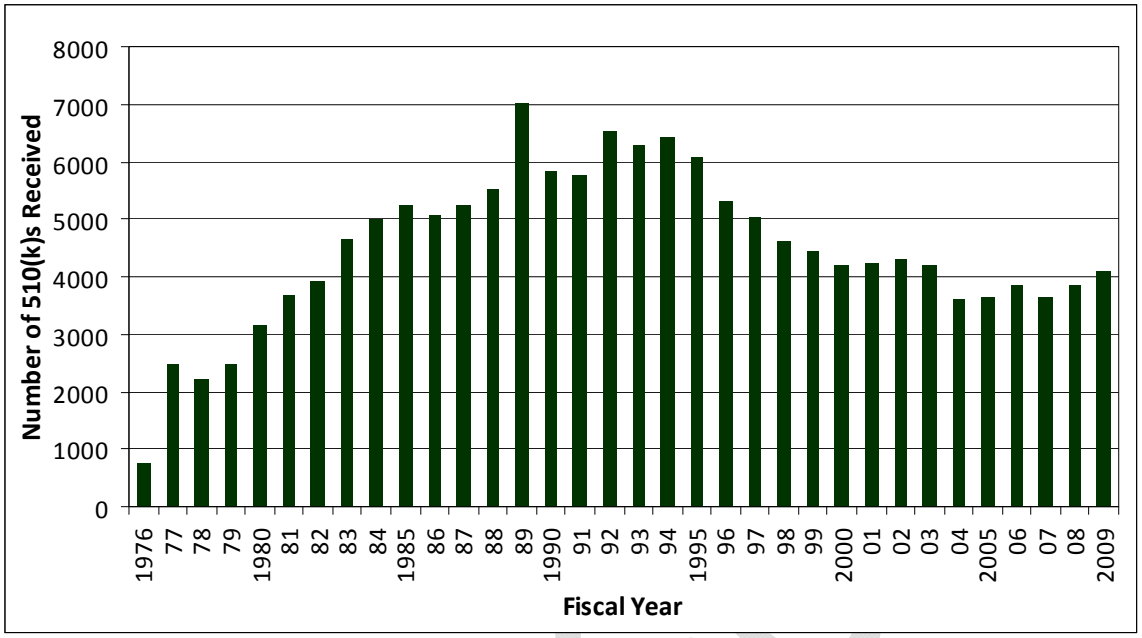
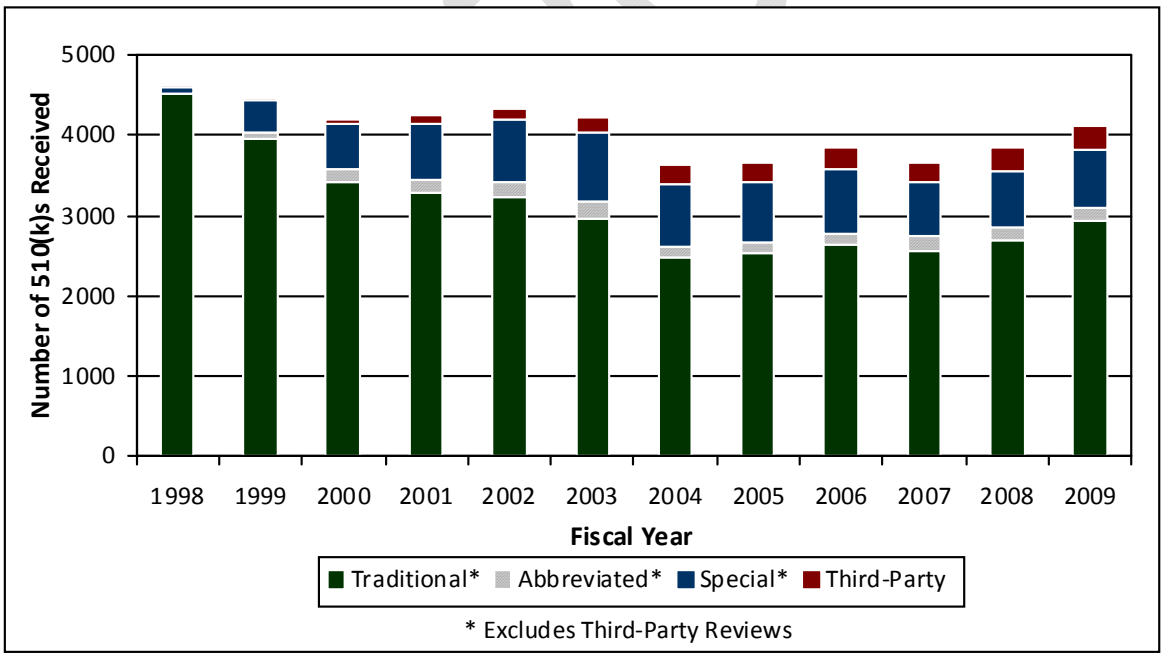


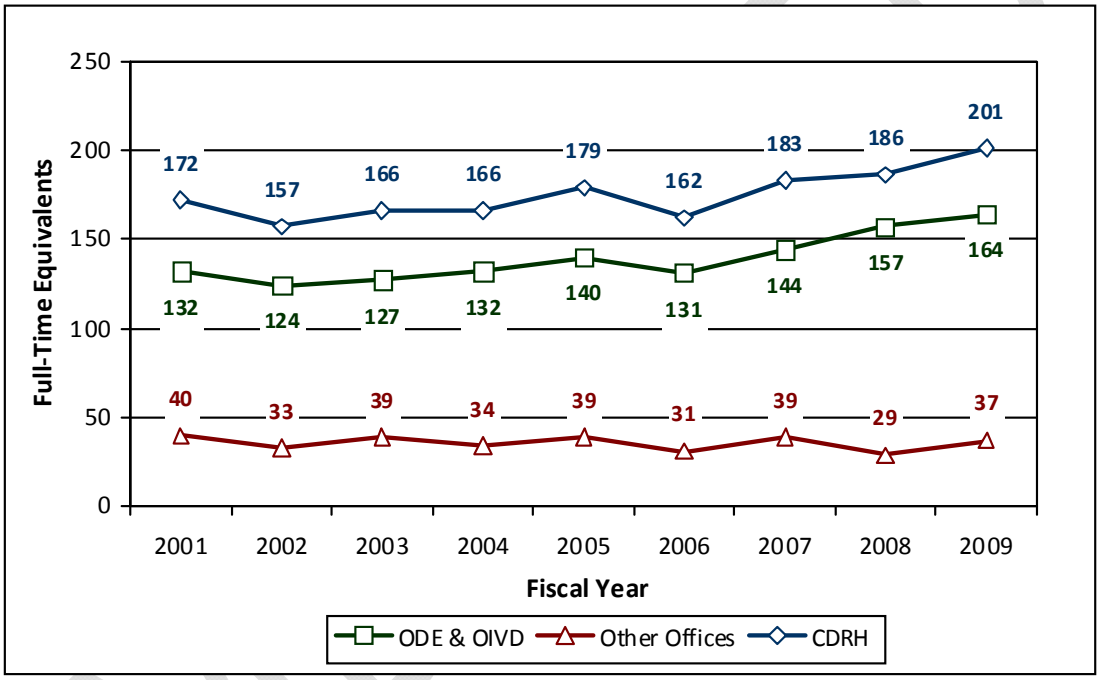
Figure 4.2. Original 510(k)s Received by CDRH by Type: FY 1998-2009



[78] The fluctuation in annual 510(k) receipts over time shown in Figure 4.1 is largely due to various regulatory and statutory changes. The notable increase in 510(k)s in 1989 was caused primarily by the change in the status of exam gloves from 510(k)-exempt to non-exempt. Immediately after this change went into effect, CDRH received over a thousand 510(k)s for exam gloves that had already been on the market. 510(k) receipts declined in the 1990s as FDA exempted most class I devices and, following the passage of FDAMA in 1997, dozens of class II devices. 510(k) receipts declined again following the passage of MDUFMA in 2002. 510(k) receipts have been increasing steadily in the past three years. Note that Figures 4.1 and 4.2 here show the number of *original* 510(k)s received each year, whereas Figure 4.2 in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making shows the number of *all* 510(k)-related submissions received.

510(k)s are reviewed by staff across two Offices within CDRH. The Office of Device Evaluation (ODE) is comprised of five divisions, with a total of 21 branches, and the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) is comprised of three divisions. Figure 4.3, below, shows the number of CDRH full-time equivalents supporting the 510(k) program, including premarket reviewers in ODE and OIVD, as well as other staff throughout the Center who periodically act as consultants on 510(k) reviews. CDRH has been increasing the size of its premarket staff over the past few years, due to increased funding from user fees and Congressional appropriations. However, staffing increases have not kept pace with the growth in total premarket workloads. Challenges related to review workloads are discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.

Figure 4.3. CDRH FTEs Supporting the 510(k) Program: FY 2001-2009



Figures 4.4 and 4.5, below, show general statistics on 510(k) decisions and the average length of review for different types of submissions.

Figure 4.4. 510(k) Decisions by Type: FY 2009 Decision Cohort [79]

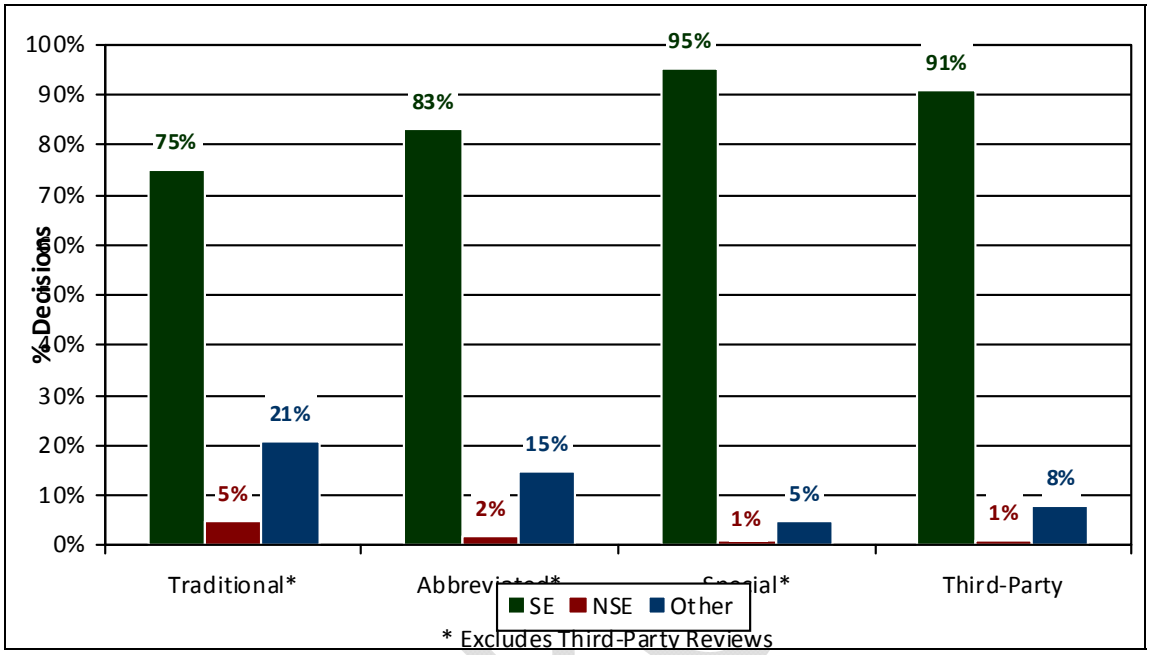
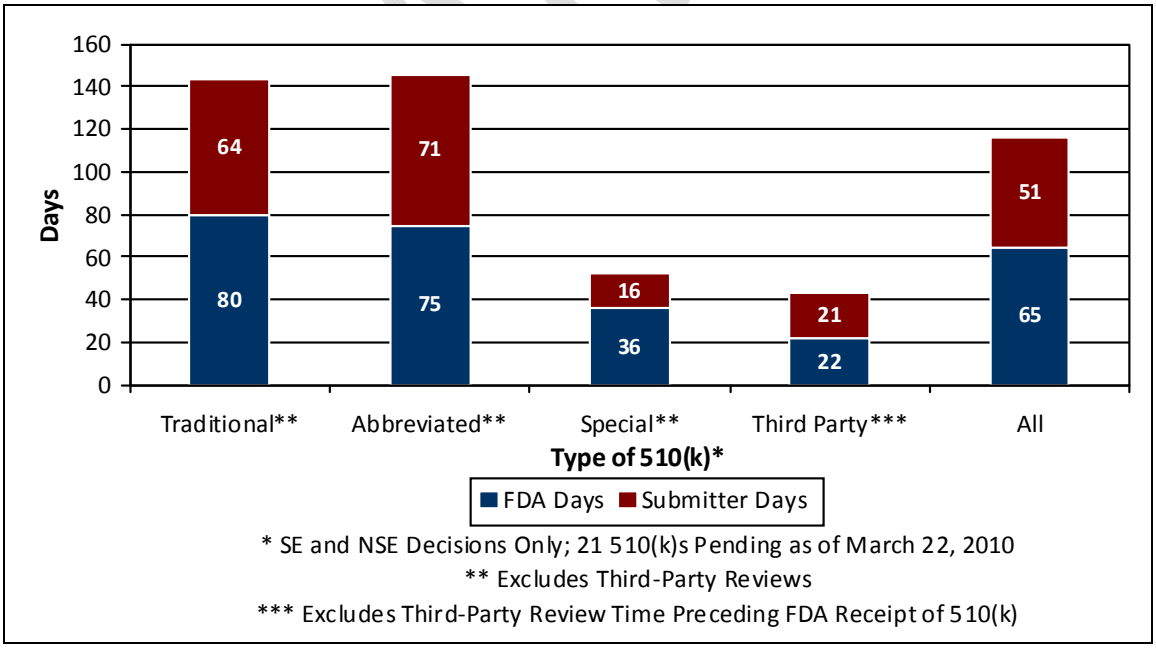


Figure 4.5. Average Time to 510(k) Decision by Type of 510(k): FY 2008 Receipt Cohort [80]



[79] Values may not sum to 100 percent due to rounding. "Other" includes withdrawn, deleted, exempt, not a CDRH-regulated device, etc.

[80] "FDA Days" refers to time during which a submission is under active review by FDA. "Submitter Days" refers to time during which a submission is "on hold" pending the receipt of additional information requested by FDA. "FDA Days" and "Submitter Days" sum to the total length of time from initial FDA receipt of a submission until issuance of a decision.

While the number of 510(k)s the Center receives annually has fluctuated since the program's inception, the program has consistently grown over time to accommodate an increasing range of device types, including low-risk devices such as crutches, higher-risk devices such as radiation therapy treatment planning systems, implanted devices such as artificial joints, and life-supporting or life-sustaining devices such as infusion pumps and ventilators. As shown in Figure 4.6, below, there has been a steady increase in the number of product codes for 510(k) devices over the past two decades, reflecting the continuing introduction of new device types into the process. Figure 4.7, below, shows that the size of 510(k)s has been increasing markedly since the early years of the program, as submissions have become more complex.

Figure 4.6. Total Number of 510(k) Product Codes: CY 1990-2009

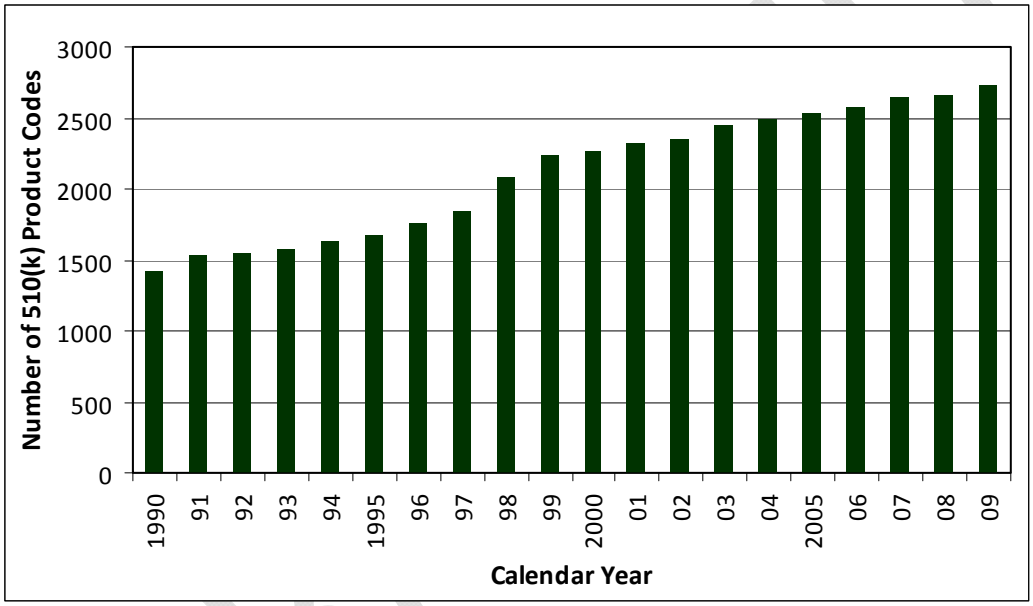


Figure 4.7. Pages per 510(k) and Total Page Volume Received: FY 1983-2008

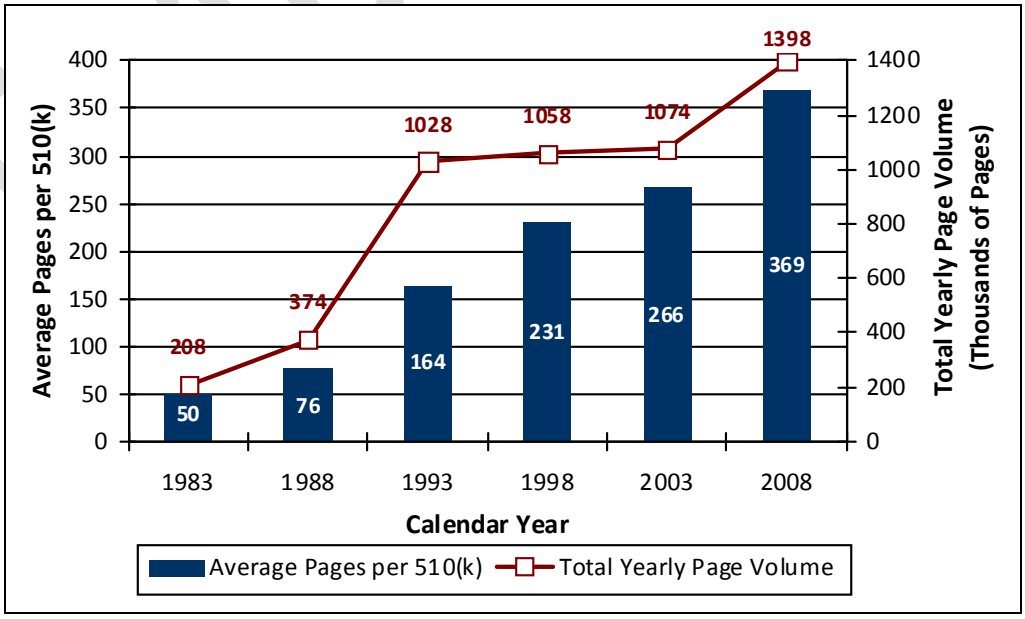


Figure 4.8, below, show that there has been a steady increase over the past several years in the average number of review cycles per 510(k), indicating a greater number of additional information requests. Figure 4.9, below, shows that, over the same time period, there has been an increase in the number of 510(k) withdrawals and deletions, which frequently occur when submissions are on hold pending receipt of requested information. These trends suggest that there is a need for increased clarity about what information submitters are expected to include in their initial 510(k) submissions.

Figure 4.8. Number of 510(k) Review Cycles: FY 2002-2008

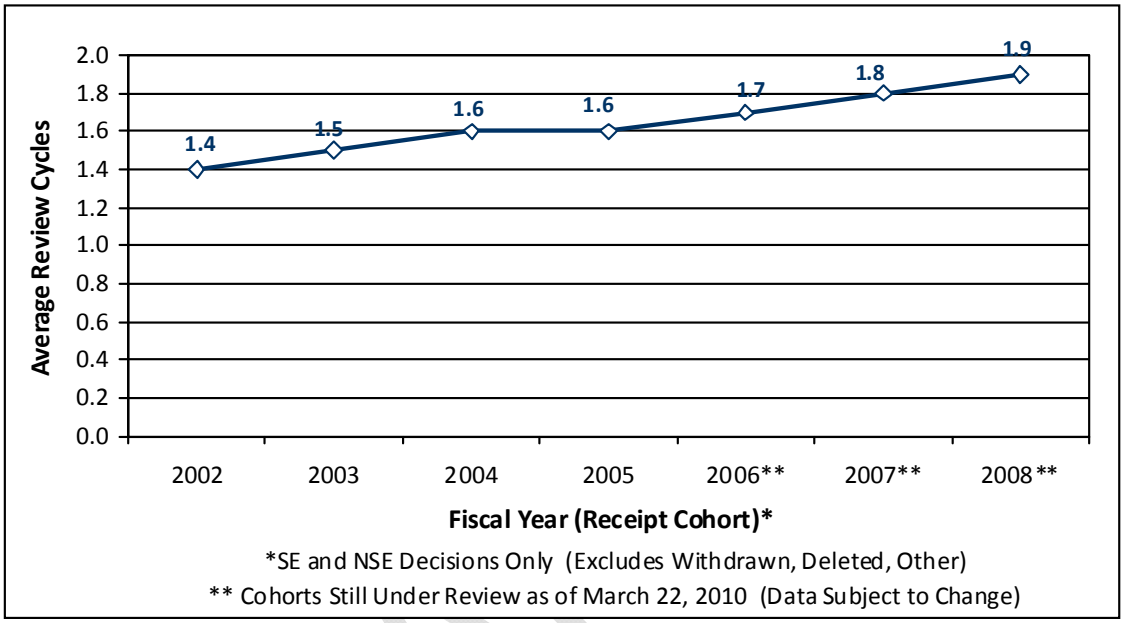
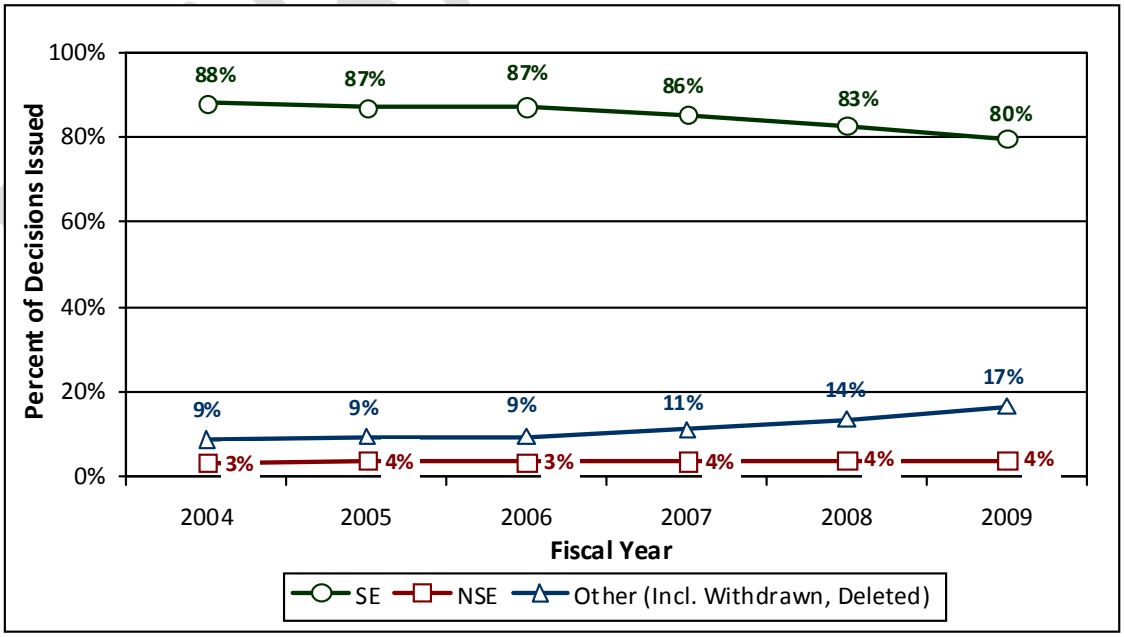


Figure 4.9. 510(k) Decisions Issued: FY 2004-2009 [81]



[81] Values may not sum to 100 percent due to rounding.

While Figure 4.10, below, shows that CDRH has been steadily improving in terms of meeting its decision performance goals, Figure 4.11 shows that the total time from 510(k) receipt to decision has gradually been increasing over the past several years.

Figure 4.10. Percent of 510(k) Decisions within 90 FDA Days: FY 2002-2008

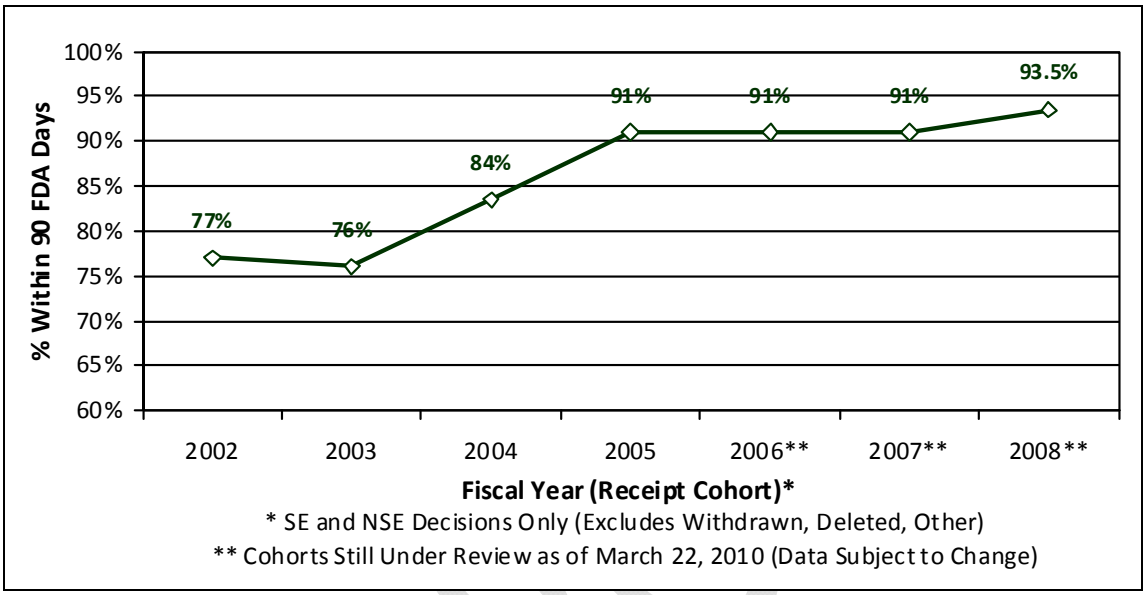
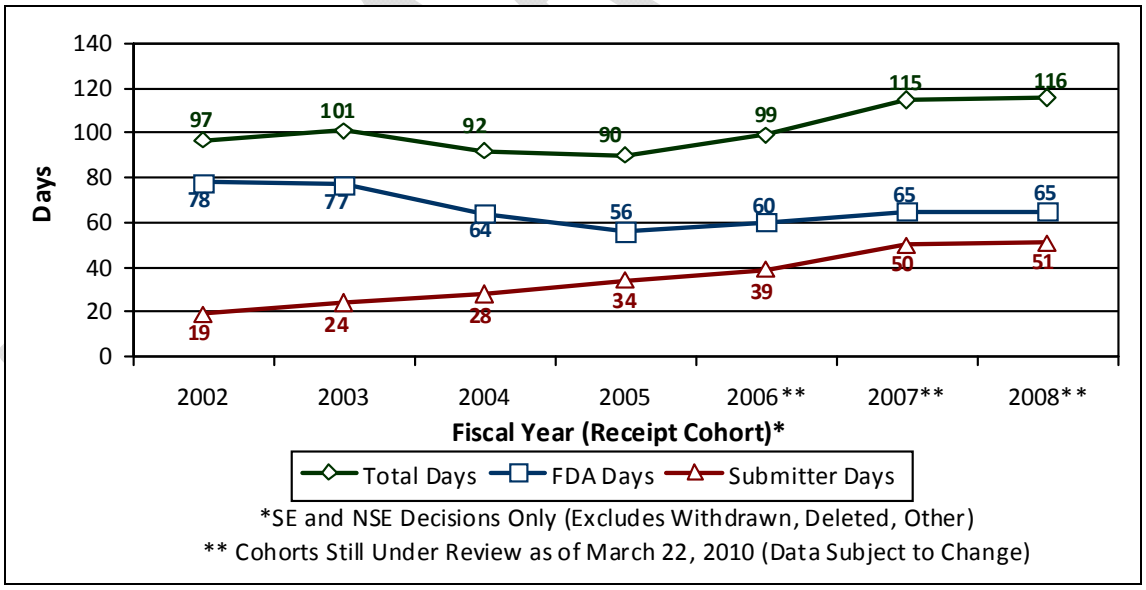


Figure 4.11. Average Time to 510(k) Decision: FY 2002-2008 [82]



Together, these various trends suggest that, as the 510(k) program has changed over time, it has become more challenging for CDRH staff and submitters alike. The 510(k) Working Group's recommendations are aimed toward addressing these challenges.

[82] "FDA Days" refers to time during which a submission is under active review by FDA. "Submitter Days" refers to time during which a submission is "on hold" pending the receipt of additional information requested by FDA. "FDA Days" and "Submitter Days" sum to the total length of time from initial FDA receipt of a submission until issuance of a decision.

5. FINDINGS AND RECOMMENDATIONS

In keeping with FDA's mission to protect and promote the public health, the aim of the 510(k) program is two-fold: (1) to assure, through a quality review process, that cleared devices provide a reasonable assurance of safety and effectiveness with general and special controls, as applicable, and (2) to foster innovation. An effective 510(k) program is predicated on three major elements. First, 510(k) decision making must be grounded in a rational, well-defined, and consistently interpreted review standard. Second, the 510(k) program must effectively support informed decision making by facilitating the collection of sufficient information to allow for well-informed, reliable decisions, and by providing an operational infrastructure and tools that enable FDA to make the best use of that information through knowledge-development and knowledge-sharing. Third, there must be appropriate systems and metrics in place to continuously assure quality, consistency, timeliness, and predictability, to the extent feasible, across the 510(k) program.

Through its discussions with Center staff and external constituencies, the 510(k) Working group made several major findings and recommendations regarding each of these elements.

5.1. A Rational, Well-Defined, and Consistently Interpreted Review Standard

The 510(k) process is meant to assure that marketed devices are assigned an appropriate, risk-based level of regulatory control to provide reasonable assurance of safety and effectiveness. As described in Section 4, above, the standard for device clearance under the 510(k) process is "substantial equivalence" to a "predicate device." However, it is challenging to apply the 510(k) review standard appropriately and consistently without a clear, coherent, and reasonable explanation of key terms in the statutory definition of "substantial equivalence," and how this review standard should operate in practice.

Section 513(i)(1)(A) of the FDCA [83]

For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term "substantially equivalent" or "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 as the predicate device, or

(ii) (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by [FDA] or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

[83] 21 USC §360c(i)(1)(A).

5.1.1. Finding: There is insufficient clarity with respect to pivotal terms in the definition of "substantial equivalence."

Recommendation: CDRH should clarify the meaning of "substantial equivalence" through guidance and training for reviewers, managers, and industry.

While CDRH's 1986 guidance (K86-3) and Congress's establishment of a statutory definition of substantial equivalence were both efforts to clarify the 510(k) review standard, key terms in this definition remain ambiguous. In particular, there is insufficient clarity about what constitutes the same versus a new "intended use," and about when "different technological characteristics" raise "different questions of safety and effectiveness." Ambiguity at these critical decision points has contributed to inconsistency in CDRH's 510(k) decision making. As the 510(k) standard has been applied to a wider range of devices over time, including increasingly varied, complex, and potentially higher-risk technologies, the need for greater clarity with respect to these terms has become even more pressing.

5.1.1.1. "Same Intended Use"

In order to make a substantial equivalence determination, CDRH must first determine whether or not the device under review has the same "intended use" as the predicate device. To allow for evolution in medical practice and device design, CDRH does not require that a new device have "indications for use" that are identical to those of the predicate device. As shown in the 510(k) flowchart,[84] a new device may have a different "Indication Statement" than the predicate device and still be determined to have the same "intended use." As long as the differences in "indications" do not "Alter the Intended Therapeutic/Diagnostic/etc. Effect" with respect to the predicate, including any impact on safety and effectiveness, the new device is considered to have the same "intended use."[85]

CDRH has exercised flexibility in construing the "intended use" of the predicate and the new device, as well as the risks that may be created due to any differences between the devices' "indications for use." However, being flexible without a clear interpretation of the terms "intended use" and "indications for use" has allowed for unpredictability: it has been difficult to consistently determine when different "indications for use" constitute a new "intended use."

The 510(k) Working Group found that there is a lack of clarity both within and outside of CDRH regarding "indications for use" and "intended use." Through its Reviewer Survey, the Working Group found that, while 96 percent of respondents in the reviewer cohort and 100 percent of respondents in the manager cohort correctly answered a question regarding what information they may consider to determine a device's "intended use," only 60 percent of respondents in the reviewer cohort and 81 percent of respondents in the manager cohort correctly indicated that a device with a new "intended use" cannot be found substantially equivalent. 28 percent of respondents in the reviewer cohort and 14 percent of respondents in the manager cohort incorrectly believed that a device with a new "intended use" could be found substantially equivalent if the device had the same technology as the predicate and the

[84] *See* page 27 of this report.

[85] Similarly, 21 CFR 807.92(a)(5) states that a 510(k) summary, if submitted, should include "A statement of the intended use of the device that is the subject of the premarket notification submission, including a general description of the diseases or conditions that the device will diagnose, treat, prevent, cure, or mitigate, including a description, where appropriate, of the patient population for which the device is intended. If the indication statements are different from those of the legally marketed device…, the 510(k) summary shall contain an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and why the differences do not affect the safety and effectiveness of the device when used as labeled."

submitter provided appropriate bench and clinical testing. In addition, when asked a question aimed at assessing respondents' understanding of the difference between "indications for use" and "intended use," only 56 percent of respondents in the reviewer cohort and 65 percent of respondents in the manager cohort answered correctly. Comments from external constituencies also reflected confusion about these terms.

Lack of a Clear Distinction Between Terms. One source of the ambiguity surrounding "intended use" is the fact that CDRH has not consistently articulated the distinction between "indications for use" and "intended use" in the context of making a substantial equivalence determination. Confusion between these terms has led to a lack of clarity about what reviewers should consider in determining whether or not a new device has the same "intended use" as the predicate to which it is compared.

The terms "intended use" and "indications for use" are not defined in the premarket notification regulations in 21 CFR 807, Subpart E. "Intended use" is defined at 21 CFR 801.4 for purposes of determining "intended use" primarily from labeling.[86] "Indications for use" is defined at 21 CFR 814.20(b)(3)(i) for the purposes of identifying the necessary components of a PMA application.[87] However, it is not clear how the agency is to apply these definitions with respect to making a substantial equivalence determination; they do not describe how differences in "indications for use" are to be assessed to determine if a new device has the same "intended use" as a predicate.

CDRH has, in *guidance*, described the terms "intended use" and "indications for use" in the context of 510(k) applications and substantial equivalence determinations. As discussed in Section 4.2.1, above, CDRH's 1986 guidance (K86-3) outlines the requirements for premarket notification review and identifies some general points CDRH considers when making a substantial equivalence determination. The guidance states that "a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found [substantially equivalent]."[88] Thus, to determine whether the new device has the same intended use as a predicate device, CDRH "assesses any difference in label indications in terms of the safety and effectiveness questions they may raise."[89]

In January 1997, CDRH issued the guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device."[90] This document acknowledges that the distinction between "indications for use" and "intended use" may be confusing. It defines "intended use" and "indications for use" using the language provided in 21 CFR 804.1 and 21 CFR 814.20, respectively.[91,92] Thus, while these regulatory

[86] 21 CFR 801.4 states, "The words *intended uses* … refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article."

[87] 21 CFR 814.20(b)(3)(i) defines "indications for use" for the purposes of submitting a premarket approval application (PMA). It states that "indications for use" are "A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."

[88] "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)," at 2-3.

[89] *Id.* at 3.

[90] "Deciding When to Submit a 510(k) for a Change to an Existing Device" (January 10, 1997). Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080243.pdf.

[91] The guidance states, "The regulatory term 'intended use' refers to the objective intent of the persons legally responsible for the labeling of the device. Intent may be determined by written expressions or may be shown by the circumstances surrounding the distribution of the device. The concept of intended use has particular relevance in determining whether a device can be cleared for marketing through the premarket notification (510(k)) process or must be evaluated in a premarket

definitions do not specifically pertain to substantial equivalence determinations, CDRH has, in guidance, adopted them within the context of determining substantial equivalence.

However, two other guidance documents — K86-3, discussed above, and "Guidance for Industry: General/Specific Intended Use"[93] — use the terms "intended use" and "indications for use" interchangeably. For example, K86-3 states, "[F]or some new devices, modifications in label indications will not be found to represent the same intended use as a predicate device, even though the intended effect of the new device is very similar to that of the predicate device. This is because *slight modifications in intended use* can be significant to the claimed effect or purpose of the predicate device."[94] In actuality, it is slight modifications in the *"indications for use"* that may affect the "claimed effect or purpose" (*i.e.*, the "intended use") of the device.

Similarly, the "General/Specific Intended Use" guidance uses the term "intended use" in its title, but states that the purpose of the guidance is to identify the general principles FDA will consider "in determining when a specific *indication for use* is reasonably included within a general *indication for use*."[95] However, the guidance further notes that CDRH issued the guidance in accordance with section 513(i)(1)(F) of the FDCA,[96] which requires FDA to issue guidance "specifying the general principles [FDA] will consider in determining when a specific *intended use* of a device is not reasonably included within a general use of such device for purposes of a determination of substantial equivalence…" (emphasis added).

Moreover, one FDA regulation uses the term "intended use" in a manner that is not consistent with its use in other agency documents. Specifically, 21 CFR 807.81(a)(3)(ii) states that a new 510(k) is required if there has been a "major change or modification in the *intended use* of the device" (emphasis added). According to the 510(k) decision-making criteria, however, a major change or modification in "intended use" would likely constitute a new "intended use" and therefore lead to an NSE determination.

A final source of confusion between the terms "indications for use" and "intended use" is CDRH's use of the "Indications for Use" form that submitters provide to the Center as part of their 510(k)s. The "Indications for Use" form was created in February 1996, when CDRH announced that it would list cleared "indications for use" in the clearance letters for devices found to be substantially equivalent. To effectuate this practice, CDRH asked each 510(k) submitter to clearly identify as part of its 510(k), on a sheet now called the "Indications for Use" form, the "indications for use" for which it was seeking a

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approval application (PMA). Manufacturers should recognize that if a particular labeling change results in a 'new' intended use for the device, the agency will find the device to be not substantially equivalent and require premarket approval." *Id.* at 10.

[92] The guidance states, "An indication for use is a 'general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the disease is intended.' The indications include all the labeled patient uses of the device, for example: the condition(s) or disease(s) to be screened, monitored, treated, or diagnosed[;] prescription versus over-the-counter use[;] part of the body or type of tissue applied to or interacted with[;] frequency of use[;] physiological purpose (*e.g.*, removes water from blood, transports blood, etc.)[;] or patient population. The indications for use are normally found in the indications section of the labeling, but indications may also be inferred from other parts of the labeling such as the precautions, warnings, or the bibliography sections. In some instances, a change in the indications for use may be a new intended use for the device, in which case, the 510(k) for the changed device would be found not substantially equivalent and a premarket approval application or a reclassification petition would be necessary." *Id*. at 24-25.

[93] "Guidance for Industry: General/Specific Intended Use" (November 4, 1998). Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm.

[94] "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)," at 7 (emphasis added).

[95] "Guidance for Industry: General/Specific Intended Use," at 1 (emphasis added).

[96] 21 USC §360c(i)(1)(F).

substantial equivalence determination. In announcing this policy, CDRH noted that, to accurately reflect the 510(k) submitter's stated "indications for use," as mutually agreed upon by the Center and the submitter, CDRH would include the form with the outgoing clearance letter.[97]

This policy notes that "[i]f modifications or deletions are made to the indications as submitted, these will be negotiated with the submitter and the cleared indications will be clearly delineated."[98] This statement implies that the "indications for use" originally proposed by the submitter on its "Indications for Use" form need not be those ultimately cleared by CDRH. Nevertheless, some reviewers mistakenly believe that if the "Indications for Use" form initially submitted for a new device is the same as the "Indications for Use" form cleared for the predicate, then the new device should automatically be deemed to have the same "Indication Statement" as the predicate. This is potentially problematic because, according to the 510(k) flowchart, if the new device has the same "Indication Statement" as the predicate, then it is automatically considered to have the same "intended use."

Contrary to this mistaken belief, CDRH's expectation is that, as part of the 510(k) review process, reviewers should establish the new device's "intended use" based on the totality of information submitted, including not only the "Indications for Use" form, but also other information contained in the product's labeling, design features, and statements made in the file. However, because of semantic confusion between the terms "indications for use," "Indication Statement," and "intended use," this approach has not consistently been put into practice. As a result, a device may be determined to have the same intended use as a predicate based on assertions by the submitter on the "Indications for Use" form, without an adequate review of other information contained in the 510(k).

- The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use," in order to reduce inconsistencies in their interpretation and application. Several public comments expressed concern that, if these two terms were combined, any proposed change in a device's label indications could be considered a change in "intended use." The Working Group recognizes the importance of providing submitters with the flexibility to propose certain changes to their labeling, without such a change necessarily constituting a new "intended use." Therefore it recommends that CDRH carefully consider what characteristics should be included under the term "intended use," so that modifications that are currently considered to be only changes in "indications for use" and that CDRH determines do not constitute a new "intended use," are not in the future necessarily construed as changes in "intended use" merely because of a change in semantics. Any change in terminology would be intended to provide greater clarity and simplicity, not necessarily to make the concept of "intended use" more restrictive. The Center should also carefully consider what it should call the existing "Indications for Use" statement in device labeling and the "Indications for Use" form currently required for all 510(k)s, in order to avoid confusion in terminology but still maintain an appropriate level of flexibility for submitters.

Insufficient Guidance for 510(k) Staff and Industry. Although K86-3 and the 1997 guidance on "Deciding when to Submit a 510(k)" have been reasonably successful in helping CDRH staff determine whether a new device has a new "intended use" in cases that are clear-cut, they do not provide enough direction to allow for consistent implementation across the board.

[97] "Indications for Use Statement" (February 6, 1996). Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080275.htm.

[98] *Id.*

In particular, it is challenging for staff to determine when the difference between a general "indication for use," such as one targeting the population as a whole, and a specific "indication for use," such as one targeting a specific subpopulation, would result in a new "intended use." For example, one device may have general indication for surgical ablation in urology, while another may have a more specific indication for surgical treatment of benign prostatic hyperplasia. Similarly, one diagnostic device may have a specific diagnostic indication, while another may have a general screening indication. As shown in the box below, CDRH has reached different conclusions under different circumstances about whether a change in indication from general to specific, or vice versa, constitutes a new "intended use." There is insufficient clarity among review staff and industry regarding when such a change is to be considered a new "intended use."

CDRH's "General/Specific Intended Use" guidance, discussed above, identifies broad principles CDRH considers in determining when a specific "indication" is reasonably included within a general "intended use" for the purposes of making a substantial equivalence determination. In general, CDRH assesses any differences in indication specificity in terms of the safety and effectiveness questions such differences may raise. However, these principles have not always been applied consistently across the Center.

Examples: General vs. Specific "Indication for Use"

Same "Intended Use." Condoms labeled with the general indication for use of prevention of sexually transmitted diseases were used as a predicate for condoms labeled to prevent transmission of HIV. In this situation, an overriding public health benefit, an established safety profile, and an identical mechanism of action were weighed against concerns regarding the level of available effectiveness data in deciding that 510(k) was the appropriate regulatory pathway for this indication for use. The Senate committee report that preceded the final FDAMA bill stated, "This determination made perfect public health sense, despite the fact that the general use labeling pre-dated the 'Medical Device Amendments of 1976' and HIV was unknown at that time."[99]

New "Intended Use." A telethermographic system is an electrically powered device with a detector that is intended to measure, without touching the patient's skin, self-emanating infrared radiation that reveals temperature variations on the surface of the body. This generic type of device may include signal analysis and display equipment, patient and equipment supports, component parts, and accessories. When indicated for adjunctive diagnostic screening for the detection of breast cancer, the device is in class I and requires a 510(k). However, when indicated for use alone in diagnostic screening for detection of breast cancer, the device is considered to have a different "intended use." With the latter indication, the device is in class III and requires a PMA.

In addition to issues related to the specificity of "indications for use," it is challenging for staff to determine when a new device feature or function would result in a new "intended use." This is particularly the case when the clinical utility or benefit of the new feature is not well-established or well-understood, making it difficult to determine whether or not it alters the intended effect of the device. Similar challenges arise when a new function moves a device from a generic "tool" indication to a particular "treatment" indication. CDRH staff have not had sufficient guidance or training to consistently determine when a new feature or function should be considered a new "intended use."

[99] S. Rep. No. 105-43 (1997), at 30.

Example: Tool vs. Therapy "Indication for Use"

New "Intended Use." Electrosurgical cutting and coagulation devices are preamendment class II devices used by cardiac surgeons to ablate tissue. These surgical tools are pen-like devices, the tips of which contain an electrode or medium through which cryothermal and radiofrequency energy are passed. These hand-held tools are used in surgical procedures to ablate different tissue types, including muscle, bowel, liver, and cardiac tissue.

New electrosurgical cutting and coagulation device designs have resulted in devices that allow for an increased area of contact between the device and the target tissue, in order to create a longer, continuous lesion at one time — instead of relying on an "ablate and drag" approach, in which the surgeon would ablate a small amount of tissue at one location and then reposition the device to a different location, while trying to ensure that the lesion is continuous. As a result of these changes, some new electrosurgical cutting and coagulation devices are no longer used as general cardiac surgical instruments. Instead, they are widely used to create long continuous lesions to treat a specific cardiac disease (namely, atrial fibrillation).

In this case, the change from a task-type or "tool" indication (*i.e.*, ablation of tissue) to a treatment-type or "therapy" indication (*i.e.*, treatment of atrial fibrillation) was determined to result in a new "intended use."

As the case study below illustrates, the lack of clarity with respect to what constitutes a new "intended use" has allowed an increasingly broad range of devices with widely varied indications for use to enter the market through the 510(k) process. In the Working Group's Reviewer Survey, 30 percent of respondents in the reviewer cohort and 33 percent of respondents in the manager cohort indicated that clinical data could be necessary to determine if a new "indication for use" constituted a new "intended use." This finding and anecdotal evidence from discussions with review staff suggest that some reviewers may apply an overly broad interpretation of "intended use." Instead of considering a device to have a new "intended use" and therefore finding that device NSE when new indications merely "*introduce* questions about safety or effectiveness different from those that were posed by the predicate device's intended use,"[100] as described in CDRH's 1986 guidance (K86-3), staff may in some cases consider such a device to have the *same* "intended use" and seek additional data to *address* any new safety or effectiveness questions raised by a new indication in the context of a 510(k) review. There currently is no uniform approach to "intended use" across the Center, which contributes to inconsistent decision making.

Case Study: "Intended Use"

Background. Prostate cancer is a prevalent yet slow-growing cancer. Prior to the 1990s, the standard treatment for prostate cancer involved either surgical removal of, or radiation to, the entire gland. The clinical community expects long-term clinical investigation to establish the safety and effectiveness of new treatments.

Cryosurgical devices are class II devices that use extreme cold to destroy tissue. These devices are used in a variety of medical specialties and are traditionally viewed as surgical tools. For internal organs such as the prostate, percutaneous probes are used to induce freezing.

[100] "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)," at 3 (emphasis added).

Issue. Prior to 1990, cryosurgery systems were indicated as tools for tissue ablation in a variety of medical disciplines, including urology and oncology. Cryosurgery of the prostate was abandoned in the 1970s, as a result of problems with a device that used a single, large-diameter cryoprobe. That device was difficult to use and caused an unacceptable rate of complications.

By 1990, new cryosurgical systems had been cleared that used multiple small probes, making prostate ablation easier. Although manufacturers aggressively sought to expand indications for their cryosurgical systems to include "treatment of prostate cancer," CDRH resisted because this treatment use carried different clinical meaning than the general, tool-type use of "tissue destruction."

However, manufacturers were successful in expanding the "tool" indication of "tissue destruction in urology" to include "removal of prostate tissue" and "prostate tumor – palliative," and a growing number of clinical researchers began to use cryosurgery as a prostate cancer treatment. Cryosurgery gradually grew in use as a prostate cancer treatment, fueled by published clinical reports, evolution of the treatment technique, and technological enhancements to the devices. Since these systems were cleared for prostate use and were becoming established for the treatment of prostate cancer, the fact that they were not specifically *indicated* for treating prostate cancer became increasingly irrelevant and difficult for CDRH to justify. In 1997, the Center reversed its stance and allowed these devices to add "treatment of prostate cancer" as an indication without its being considered a new "intended use."

Each of these incremental changes in indication was cleared without clinical data. CDRH did not specifically evaluate the safety and effectiveness of cryosurgical devices in prostate cancer treatment before allowing them to be marketed for this use.

Impact. As documented in the scientific literature, many problems arose as cryosurgery initially went into widespread use as a prostate cancer treatment.[101] In response to these early problems, treatment technique and device design have since been refined. If prospective studies had been performed prior to marketing, it is likely that these problems could have been identified and corrected earlier, and early patients could have been provided with more complete information about the risks and benefits associated with use of the devices.

Although cryosurgery remains in use as a prostate cancer treatment, it has not been fully adopted in mainstream urologic practice. According to the Agency for Healthcare Research and Quality, evidence on the effectiveness of cryosurgery as a prostate cancer treatment is of low quality.[102] Cryosurgery has not been recognized by the American Urological Association as a recommended therapeutic option for prostate cancer.[103] The Centers for Medicare and Medicaid Services (CMS) were slow to reimburse for the use of these cryosurgical devices for treatment of prostate cancer; reimbursement was not effective until 2001.[104]

[101] *See, e.g.,* Zippe, et al., "Cryosurgery of the Prostate: Techniques and Pitfalls," *Urol. Clin. N. Amer.*, Vol. 23, No. 1 (February 1996). *See also,* Pisters, et al., "Efficacy and Complications of Salvage Cryotherapy of the Prostate," *J. Urol.*, Vol. 157, No. 3 (March 1997), pp. 921-925.

[102] Agency for Healthcare Research and Quality, "Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer," *Comparative Effectiveness Review*, No. 13 (February 2008). Available at http://effectivehealthcare.ahrq.gov/repFiles/2008_0204ProstateCancerFinal.pdf.

[103] American Urological Association, "Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update" (2007/2009). Available at http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf.

[104] Centers for Medicare and Medicaid Services, *Medicare Hospital Manual*, Transmittal 774 (June 11, 2001). Available at http://www.cms.hhs.gov/transmittals/downloads/R774HO.pdf.

- The 510(k) Working Group recommends that CDRH develop or revise existing guidance to clearly identify the characteristics that should be included in the concept of "intended use."

- The 510(k) Working Group further recommends that CDRH provide training for reviewers and managers on how to determine "intended use." Such training should clarify the elements of a device application that should be considered when determining the "intended use," *e.g.*, product labeling, device design (explicit or implied), literature, and existing preclinical or clinical data. Training on "intended use" should also be provided to industry.

Off-Label Use. According to section 513(i)(E) of the FDCA,[105] "any determination by [FDA] of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k)."[106] However, there are situations in which CDRH has reason to believe that a device may be intended for a use other than what the proposed labeling suggests.

CDRH's primary mechanism for addressing anticipated off-label use is its authority to clear a device as "substantially equivalent with limitations," thereby requiring, under certain circumstances, that the manufacturer include "a statement in labeling that provides appropriate information" regarding an off-label use.[107,108] CDRH may, for example, require the manufacturer to include in its product labeling a statement that the safety and effectiveness of the device for the off-label use have not been established. CDRH may also require the manufacturer to include in its labeling adverse event information with respect to the off-label use, to the extent that such information is available. In order to make use of its SE with limitations authority, CDRH must consider: (1) whether there is a "reasonable likelihood" that the device will be used for an intended use not identified in the proposed labeling for the device; and (2) if such use could cause harm.[109] Center staff report that it can be challenging to determine whether or not an off-label use could cause harm, because of potential limitations in the data they can require as part of a 510(k) review pertaining to a use other than the device's "intended use."

Further, it is unclear if SE with limitations provides sufficient protections against potentially harmful off-label use. Concerns have been raised about the effectiveness of labeling to mitigate risks associated with device use, in part because patients and practitioners often do not have ready access to labeling at the time of use, and also because it may be difficult for users without specialized training to understand labeling that is written in very technical language. Table 5.1, below, shows the mean rate of adverse event reports (also called Medical Device Reports (MDRs)) per 510(k) for various types of cleared devices. These data suggest that devices that have been found SE with limitations are associated with more adverse event reports, on average, than other cleared devices. Further analysis will be needed to validate this apparent trend and determine its root cause.

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[105] 21 USC §360c(i)(E).

[106] Labeling includes "all labels or other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." Section 201(m) of the FDCA (21 USC §321(m)).

[107] *See* section 513(i)(1)(E) of the FDCA (21 USC §360c(i)(1)(E)).

[108] For more information on the procedures for issuing an "SE with limitations" decision, *see* "Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1)."

[109] *See* section 513(i)(1)(E) of the FDCA (21 USC §360c(i)(1)(E)).

Table 5.1. Mean MDR Rate per 510(k) by Decision Type [110]

Decision Type	Total 510(k)s	All MDRs	Death	Injury	Malfunct.
SE with limitations	105	6.41	0.24	2.75	3.32
SE	14,287	2.09	0.03	0.98	1.02
CLIA SE [111]	982	1.95	0.00	0.10	1.83
SE – Kit [112]	24	0.48	0.05	0.38	0.05
NSE	604	0.00	0.00	0.00	0.00
Other [113]	2,330	0.14	0.00	0.13	0.01
All	18,332	2.10	0.02	0.85	1.16

In some circumstances, there may be reason to believe that a device's *primary* "intended use" is an off-label use that the proposed labeling does not accurately reflect. As highlighted in the box below, there may be situations in which a device is labeled and cleared for a use that is not the actual use for which the device is intended. In such a case, CDRH would not have made an informed decision about whether or not the new device is safe and effective for its true (*i.e.*, off-label) "intended use." CDRH could engage in rule-making to make such a product a restricted device;[114] however, that process can take several years to complete.

Example: Off-Label Use

Bone void fillers are class II devices that are intended to fill bony defects. In a 510(k) for a biphasic composite device, the submitter claimed substantial equivalence to a predicate bone void filler. Much of the information provided in the 510(k) was consistent with that typically provided for bone void fillers. However, the device had a non-typical, biphasic structure, and the data provided in the submission were from an animal study in which the device was utilized as an osteochondral plug to fill a focal defect in the articular cartilage of the femoral condyle. These two elements suggested that the device might be used for a different "intended use" than what the labeling suggested. Further, the device was being promoted and used as an osteochondral/chondral replacement device outside the U.S.

Utilization of the device for filling of a focal defect in the articular cartilage is a higher-risk, postamendment class III usage and would require review and approval under the PMA pathway. However, because the submitter only stated the device was intended for use as a bone void filler and

[110] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "MDR rate" refers to the number of MDRs for a device per 1,000 days on the market. Note that MDRs frequently do not cite the 510(k) number of the device associated with the adverse event; therefore, these data likely underestimate the total number of MDRs per device.

[111] "CLIA SE" refers to devices that receive a Clinical Laboratory Improvement Act (CLIA) categorization along with the SE decision.

[112] "SE – Kit" refers to devices that are cleared as a kit, *i.e.*, preamendment, exempt, or cleared devices packaged together without a new intended use. *See* "Kit Certification for 510(k)s." Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080213.htm.

[113] "Other" includes withdrawn, deleted, exempt, not a CDRH-regulated device, etc.

[114] *See* sections 502(q) and 502(r) of the FDCA (21 USC §352(q) and 21 USC §352(r), respectively).

was not intrinsic to the stability of the bony structure, it was not possible to consider the suspected off-label use in the review of the 510(k). Thus, the device's safety and effectiveness for the latter use were not evaluated.

After the device was cleared, CDRH found that the manufacturer was, in fact, marketing it for the off-label use of filling osteochondral defects, for articular repair or filling an osteochondral harvest site. CDRH is exploring potential changes to the labeling of the device to clarify that its safety and effectiveness for this use have not been established.

- The 510(k) Working Group recommends that CDRH explore the possibility of pursuing a statutory amendment to section 513(i)(E) of the FDCA[115] that would provide the agency with express authority to consider an off-label use, under certain limited circumstances, when determining the "intended use" of a device under review through the 510(k) process. Such circumstances would include the availability of compelling evidence that the primary use of the marketed device will be off-label. If the Center were to pursue such an approach, it should also clearly define what type and level of evidence would be sufficient to determine that the off-label use is the primary intended use.

5.1.1.2. "Different Questions of Safety and Effectiveness"

After CDRH has determined that a device under review has the same intended use as the predicate device, it must determine whether the device has the same or different "technological characteristics" in comparison to the predicate. If the device has different "technological characteristics," CDRH must determine whether or not the device under review is as safe and effective as a legally marketed device and whether it raises "different questions of safety and effectiveness" than the predicate.

Section 513(i)(1)(B) of the FDCA[116] states that "the term 'different technological characteristics' means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device." CDRH has provided examples of "technological characteristics" and "technological differences" in regulations[117] and guidance.[118] However, it is not clear in the statute or FDA regulations what differences raise "different questions of safety and effectiveness" that may preclude a finding of substantial equivalence.

The 510(k) Working Group found that there is insufficient clarity and consistency within CDRH regarding when different "technological characteristics" raise "different questions of safety and effectiveness." Through its Reviewer Survey, the Working Group found that 41 percent of respondents in the reviewer cohort and 43 percent of respondents in the manager cohort found it "very difficult" or "somewhat difficult" to make an NSE determination based on "different questions of safety and effectiveness."

[115] 21 USC §360c(i)(E).

[116] 21 USC §360c(i)(1)(B).

[117] 21 CFR 807.92(a)(6) states that if a device under review "has different technological characteristics from the predicate device," then the 510(k) summary, if submitted, must include a "summary of how the technological characteristics of a device compare to a legally marketed device…." The regulation lists design, material, chemical composition, and energy source as examples of "technological characteristics."

[118] "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)" states, "Technological differences may include modifications in design, materials, or energy sources; for example, changes in the power levels of electrical surgical instruments, the use of new reagents in in vitro diagnostic devices, the use of new materials in orthopedic implants, and the use of new battery designs in implanted pacemakers."

Inconsistent Terminology. One factor that may contribute to this lack of clarity is the inconsistency between the language in the statute and the language in the 510(k) flowchart[119] with respect to "technological characteristics." While both the FDCA and FDA regulations refer to "different technological characteristics" and "different questions of safety and effectiveness," the 510(k) flowchart refers to "new characteristics" and "new types of safety or effectiveness questions." There is concern among CDRH staff that these and other differences between the 510(k) flowchart and the statutory definition of substantial equivalence make it challenging to consistently apply the statutory review standard to determine when "different technological characteristics" raise "different questions of safety and effectiveness" when comparing the "technological characteristics" of a new device to those of a predicate.

- The 510(k) Working Group recommends that CDRH revise existing guidance to reconcile the language in its 510(k) flowchart with the language provided in section 513(i) of the FDCA[120] regarding "different technological characteristics" and "different questions of safety and effectiveness."

Insufficient Guidance for 510(k) Staff and Industry. Although CDRH provides in its 1986 guidance (K86-3), examples of various technological differences that would result in SE or NSE decisions, the examples do not reflect the complex technologies of more modern devices. Moreover, the guidance does not fully articulate a clear standard that may be applied consistently by reviewers and managers in determining which "technological characteristics" to consider in their decision making, and how to determine whether such characteristics raise "different questions of safety and effectiveness."

This lack of clarity has contributed, in some circumstances, to inconsistency in CDRH's decision making. In the Working Group's Reviewer Survey, CDRH reviewers were asked to select, from a list of nine options, examples of device changes that would constitute a change in "technological characteristics." As shown in Table 5.2, below, responses varied in both the reviewer and manager cohorts.

Table 5.2. Reviewer Survey Responses: Technological Characteristics

Question: Which of the following represent a change in the technological characteristics from the predicate device to the subject device? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Replacing a digital x-ray detector's wired network connection with a wireless one.	83.5% (157)	95.2% (20)
B. Changing a catheter's material from silicone to polyvinyl chloride (PVC).	75.0% (141)	76.2% (16)
C. Moving a warning label from the back of an automated external defibrillator (AED) to the front of the device.	1.6% (3)	0.00% (0)
D. Adding an emergency stop button to a device.	51.1% (96)	42.9% (9)

[119] *See* page 27 of this report.
[120] 21 USC §360c(i).

Option	Reviewers % Selected (#)	Managers % Selected (#)
E. A manufacturer of a central venous catheter that is sold to a distributor submits a 510(k) for the same product.	2.7% (5)	0.0% (0)
F. Updating the software in a device to run on Windows 7 instead of Windows XP.	50.0% (94)	38.1% (8)
G. Changing the recommended sterilization method for a device.	50.0% (94)	57.1% (12)
H. Adding a coating to inhibit the growth of microorganisms on the surface of the device.	93.1% (175)	85.7% (18)
I. Adding a signal processing algorithm to assess brain wave activity to an electroencephalograph (EEG).	89.9% (169)	90.5% (19)

Respondents were also asked to select, from a list of six options, examples of technological changes that would raise "new types of safety and effectiveness questions." As shown in Table 5.3, below, responses varied in both cohorts.

Table 5.3. Reviewer Survey Responses: "New Types of Safety or Effectiveness Questions"

Question: Which of the examples below represent a new type of safety or effectiveness question(s)? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. An ultrasound device cleared for imaging of a fetus has a new feature to assess the stiffness of coronary arteries to determine if there is coronary artery disease.	87.0% (160)	85.7% (18)
B. A surgical device cleared to cut and ablate tissue using RF (radiofrequency ablation) is the predicate for a microwave thermotherapy system to necrose tissue.	71.2% (131)	52.4% (11)
C. A manual medical device such as a colonoscope is redesigned to be fully automated.	78.3% (144)	38.1% (8)
D. A class I medical device exempt from premarket notification requirements where the sponsor intends to coat this device with a drug to reduce inflammation.	91.8% (169)	90.5% (19)
E. A roller cardiopulmonary bypass blood pump (a device that uses a revolving roller mechanism to pump the blood during cardiopulmonary bypass surgery) is modified to use a centrifugal pump that uses centrifugal force to control blood flow.	59.8% (110)	47.6% (10)

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
F. A battery-operated powered wheelchair cleared to provide mobility to persons restricted to a sitting position is modified to add a stair-climbing capability.	79.9% (147)	52.4% (11)

As illustrated in the case study below, inconsistent interpretation of when a change in "technological characteristics" may raise "different questions of safety and effectiveness" can have a significant public health impact.

Case Study: "Different Questions of Safety and Effectiveness"

Background. Dental handpieces are powered handheld devices that are used to cut, smooth, and polish tooth structure, and to cut bone in the maxillofacial region. They are preamendment devices that are currently classified as reserved class I devices, *i.e.*, class I devices that are not 510(k)-exempt.[121]

Issue. Electric dental handpieces were cleared through the 510(k) process using an air-driven dental handpiece as the predicate. Compared to the predicate, an electric dental handpiece has the same intended use and a similar overall device design. The primary distinction between the two devices is the use of an electrically powered motor instead of an air turbine.

Although this represented a "different technological characteristic," it was not believed at the time of clearance that it would affect safety or effectiveness.

Impact. After electric dental handpieces were cleared, FDA began to receive MDRs documenting serious patient injuries, including third degree burns, due to rapidly occurring overheating of these devices. With low- and high-speed air-driven dental handpieces, the performance of the device would noticeably worsen if there were maintenance issues such as a dull bur or worn or clogged gears or bearings. If an electric handpiece is worn or clogged, on the other hand, the electric motor sends increased power to the handpiece head or attachment in order to maintain handpiece performance. This increased power can rapidly generate heat at the head of the handpiece attachment.

FDA issued a public health notification regarding patient burns from electric dental handpieces in December 2007.[122]

- The 510(k) Working Group recommends that CDRH revise existing guidance to provide clear criteria for identifying "different questions of safety and effectiveness" and to identify a core list of technological changes that generally raise different questions (*e.g.*, a change in energy source, a different fundamental scientific technology).

[121] FDA maintains a list of reserved devices, class I devices that remain subject to premarket notification, at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/3151.cfm.

[122] "FDA Public Health Notification: Patient Burns from Electric Dental Handpieces" (December 12, 2007). Available at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062018.

- The 510(k) Working Group further recommends that CDRH develop and provide training for reviewers and managers on how to determine whether a 510(k) raises "different questions of safety and effectiveness." Training on "different technological characteristics" and "different questions of safety and effectiveness" should also be provided to industry.

5.1.2. Finding: CDRH's current practice allows for the use of some types of predicates that may not be appropriate.

Recommendation: CDRH should explore the development of guidance and regulation to provide greater assurance that any comparison of a new device to a predicate is valid and well-reasoned.

While the PMA process requires each applicant to independently demonstrate a reasonable assurance of the safety and effectiveness of its device for its indications for use, the 510(k) standard of substantial equivalence to a predicate allows a 510(k) submitter to rely on the fact that, under general and applicable special controls, there is a reasonable assurance that the predicate is safe and effective for its intended use. In order for such reliance to be meaningful, CDRH must have an adequate understanding of and confidence in the predicate's safety and effectiveness, as well as confidence that the comparison *itself* is a valid one. When a predicate has a well-established risk/benefit profile and is generally well-regarded by the health care community, such a comparison, with sufficient information, can provide reasonable assurance that the new device, subject to general and applicable special controls, is safe and effective for its intended use. However, concerns have been raised that current FDA regulations, guidance, and practice may allow for some types of predicate comparisons that are insufficient to *consistently* provide such assurance.

As discussed in Section 4, above, 510(k) submitters may cite as a predicate any device legally marketed in the U.S. that is not subject to premarket approval, including:

- A device that was legally marketed prior to May 28, 1976 (a preamendment device);
- A device that has been reclassified from class III to class I or II (including a device that has been classified through the de novo classification process);
- A device that has been cleared through the 510(k) process;
- A legally marketed 510(k)-exempt device.

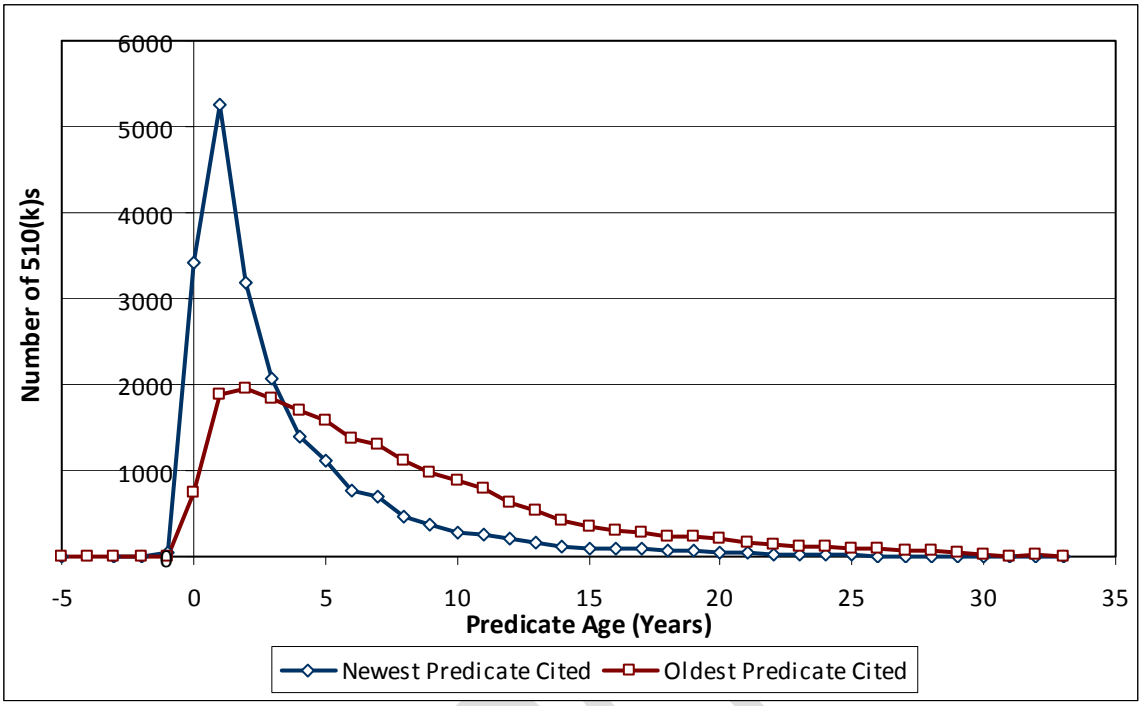
A device that has been removed from the market at FDA's initiative or that has been determined to be adulterated or misbranded by judicial order may not serve as a predicate.[123]

5.1.2.1. Concerns about Predicate Quality

Concerns have been raised that, because any legally marketed device not subject to premarket approval may be used as a predicate, a submitter may cite as a predicate a device whose safety and/or effectiveness may be questionable. For example, a predicate may be an older device no longer relevant to current standards of care. Figure 5.1, below, shows the age of predicates and other related submissions cited in the 510(k)s in the Working Group's data set. While the majority of these 510(k)s cited related submissions devices that were relatively new, roughly 25 percent cited as their most recent related submission a device that was cleared at least five years before the time of submission of the new 510(k), and roughly 8 percent cited as their most recent related submission a device that was cleared at least 10 years before the time of submission of the new 510(k).

[123] Section 513(i)(2) of the FDCA (21 USC §360c(i)(2)).

Figure 5.1. 510(k) Predicate Age [124]



Predicate age is not, in and of itself, necessarily a cause for concern. Using an older predicate may be appropriate for technologies that have not changed significantly over time, as noted in many of the public comments the 510(k) Working Group received. There are also cases in which older devices continue to be well-regarded in practice generally, or have unique benefits in comparison to newer devices, such as lower cost or design attributes that make them well-suited for a particular patient population.

However, in a number of areas, device performance has improved so dramatically that older devices are no longer in use or are widely recognized as substandard. Although the 510(k) process is meant to facilitate incremental improvements in device design over time,[125] submitters sometimes cite poorly performing predicates, including devices that have been withdrawn from the market. For example, CDRH continues to receive 510(k)s for new orthopedic devices that cite a 1979 cervical vertebrae plate

[124] Data shown are from CDRH's databases; however, the data set used in this analysis is slightly different than the data set described in Section 3.4.2. The data set used in this analysis includes 510(k)s received from 2004 through 2009. "Predicate cited" refers to the predicate(s) and other related submission(s) listed by a submitter in its 510(k). Note that sometimes review staff, in collaboration with the submitter, identify a different predicate(s) for comparison during the 510(k) review process; therefore, the predicate(s) originally cited by the submitter may not be the one(s) on which the substantial equivalence determination is ultimately based. "Predicate age" was calculated by subtracting the final decision date of the related submission from the new 510(k)'s date of submission. Negative predicate age indicates that the submitter referenced a device that was not yet cleared at the new 510(k)'s date of submission (*e.g.*, a device under concurrent review).

[125] The legislative history surrounding the passage of SMDA states, "The Committee intends that the prevailing level of safety and effectiveness must be for the devices being marketed with the same intended use, not for all devices currently marketed. For example, new bedpans should be capable of being used with the same assurance of safety and effectiveness as other bedpans now marketed, and new medical laser instruments should be evaluated on the basis of the safety and effectiveness as other medical laser instruments being marketed. In this way, the standard for safety and effectiveness in a determination of substantial equivalence will evolve slowly as the prevailing level on the market changes, rather than being tied solely to comparison with a pre-1976 device." H.R. Rep. No. 101-808, 101st Cong. 2d Sess. (1990), at 25.

which is no longer marketed and whose mechanical properties are lower than those of the weakest plates in use today. Further, a submitter is permitted to cite as a predicate a device that has been recalled by the manufacturer due to safety concerns. Among the 510(k) submissions that were received in 2009, 29 percent of the predicates cited were devices that were not registered and listed in either 2009 or 2010. It is not clear how many of these cited devices had been removed from the market for safety and/or effectiveness issues.

One way to address concerns about device performance is through the development and use of medical device consensus standards with clear pass/fail performance criteria. CDRH has been and will continue to be actively involved in this area; however, there are many device types for which FDA-recognized consensus standards do not currently exist.

Another significant source of concern is that, in most cases, the predicate device was itself cleared through the 510(k) process, and therefore was not required to have an independent showing of safety and effectiveness. A determination of substantial equivalence allows a new device to "piggy-back" on the fact that, under general and applicable special controls, there is a reasonable assurance that the predicate device is safe and effective for its intended use. However, the reliability of this determination becomes increasingly tenuous as the "distance" (*i.e.*, the number of intervening predicates) between a new device and the "original" predicate (*i.e.*, a device whose safety and effectiveness were independently demonstrated) grows.[126] In some cases, the "original" predicate is a preamendment device that was classified on the basis of experience with the marketed device, but without an independent study demonstrating safety and effectiveness.

As Figure 5.1, above, shows, most 510(k)s cite predicates that are only a few years old. However, due to limitations in CDRH's current data systems (described further in Section 5.2.2.2, below), it is not feasible to conduct an analysis of the number of intervening predicates between the new device and the "original" predicate. While the risks and benefits of many devices are well-understood because of long-term market experience or because they use relatively simple technologies, some newer and more complex devices may have risks that, without an independent demonstration of safety and effectiveness, have not been adequately characterized. In addition, CDRH's postmarket surveillance systems, while valuable, are not designed to fully evaluate the safety and effectiveness of devices on the market. They are designed to identify safety signals and monitor device performance in the marketplace, but they have important limitations.

- The 510(k) Working Group recommends that CDRH consider developing guidance on when a device should no longer be available for use as a predicate because of safety and/or effectiveness concerns. It is expected that such a finding would be an uncommon occurrence. Any factors set forth in guidance regarding when a device should no longer be used as a predicate should be well-reasoned, well-supported, and established with input from a range of stakeholders, and unintended consequences should be carefully considered.

[126] Devices frequently evolve incrementally through multiple "generations." In other words, Device A may be found SE to Device B, which in turn had been found SE to Device C, which in turn had been found SE to Device D, etc. There may be many such "generations" between a new device and a device for which there has been an independent demonstration of safety and effectiveness.

5.1.2.2. Rescission Authority

The concerns about predicate quality described above are compounded by the fact that FDA has not provided clarity regarding the circumstances under which it might exercise its authority to rescind or modify the scope of a device clearance under section 510(k).

The FDCA is silent with respect to rescission or modification of a device clearance under section 510(k). However, agencies have inherent authority to reconsider their decisions in certain circumstances, such as where there has been fraud or error, and to rectify their mistakes.[127] FDA has, to date, rescinded a limited number of 510(k) decisions. The agency has also issued a limited number of partial rescissions modifying the cleared indications for use or technological characteristics of devices, though the affected 510(k) holders have given their consent to such modifications. In 2001, FDA issued a proposed rule on the rescission of SE decisions and procedures for rescissions and appeals.[128] FDA never issued a final rule.

To date, FDA has largely limited its rescission of 510(k)s to situations involving fraud. Without a rescission regulation, it is not clear to Center staff or industry what other circumstances might warrant a rescission, such as specific concerns about the safety and/or effectiveness of a marketed device.

- The 510(k) Working Group recommends that CDRH consider issuing a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of its authority to fully or partially rescind a 510(k) clearance. As part of this process, the Center should also consider whether additional authority is needed.

5.1.2.3. Use of "Split Predicates" and "Multiple Predicates"

As shown in Figure 5.2, below, many 510(k)s cite more than one predicate device. A submitter may cite more than one predicate for one of several reasons. In some cases, the submitter lists more than one potential predicate in its 510(k), but the ultimate substantial equivalence determination relies on only one of the predicates listed. In other cases, many devices are bundled into a single submission, as described in Section 4.3.4.2, above, with a unique predicate for each device.

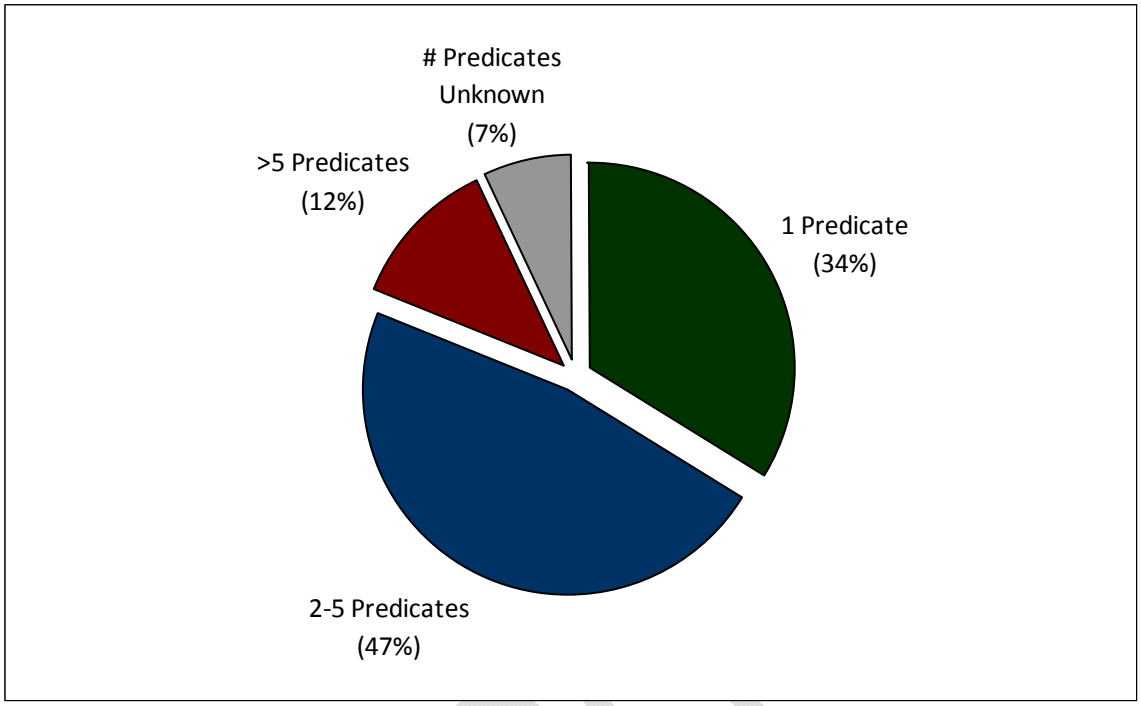
In still other cases, the submitter cites more than one predicate because no *single* predicate exists for the new device. For example, some devices, such as multi-parameter monitoring systems, combine the functions of several devices (*e.g.*, combining an electrocardiograph and a blood pressure monitor into a single device that performs the intended functions of both devices). For these devices, a submitter may seek to compare its device to more than one predicate and demonstrate that each functional component of the new device is substantially equivalent to its corresponding predicate. This practice is known as the use of "multiple predicates." Historically, CDRH has acknowledged the use of "multiple predicates" in this way as an acceptable practice.[129]

[127] *See, e.g., Sunday Sch. Bd.* v. *United States Postal Serv.*, 1999 U.S. App. Lexis 11061 (D.C. Cir 1999), *American Therapeutics, Inc.* v. *Sullivan*, 755 F. Supp. 1, 2, (D.D.C. 1990).

[128] *See* 66 Fed. Reg. 3523 (Jan. 16, 2001).

[129] "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)" describes the review of "new devices that are combinations of old devices" as follows: "A new device is a so-called 'combination' device when it claims to have the same intended uses as two or more different types of predicate devices. Normally, this is achieved by combining two or more predicate devices into a device that is sold as a unit, *e.g.*, a urinary catheter may incorporate a temperature measuring device;

Figure 5.2. Number of Predicates Cited [130]



The concept of "multiple predicates," as described above, is frequently confused with the concept of a "split predicate." The term "split predicate" refers to a situation in which a 510(k) submitter is attempting to "split" the 510(k) decision-making process by demonstrating that the new device has the same "intended use" as one predicate and the same "technological characteristics" as another. This practice is akin to combining different attributes of two or more devices into a single, nonexistent predicate device that may bear little resemblance to the device under review or to any marketed device. Concerns have been raised that the use of a "split predicate" may not allow for a valid comparison of safety and effectiveness because no such device exists, either in part or in whole, and there is therefore no real-world information about its risks and benefits.

There are differences of opinion among CDRH's review staff regarding the validity of using a "split predicate," which has led to inconsistency in the Center's treatment of 510(k)s that have cited a "split predicate." Answering a question about "split predicates" in the Working Group's Reviewer Survey, 34 percent of respondents in the reviewer cohort and 20 percent of respondents in the manager cohort indicated that it was acceptable to use one predicate for an "intended use" comparison and a second predicate for a comparison of "technological characteristics."[131]

or a cardiac monitor, electrocardiograph, and blood pressure computer that were sold separately prior to May 28, 1976, might be combined into one electronic monitoring device."

[130] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Predicates cited" refers to the predicate(s) and other related submission(s) listed by a submitter in its 510(k). Note that sometimes review staff, in collaboration with the submitter, identify a different predicate(s) for comparison during the 510(k) review process; therefore, the predicate(s) originally cited by the submitter may not be the one(s) on which the substantial equivalence determination is ultimately based. "Unknown" indicates missing data.

[131] *See* Appendix D for a full listing of questions and responses from the Reviewer Survey.

While comments from industry generally recommended that CDRH continue to allow submitters to cite more than one predicate, comments specifically regarding "split predicates" varied. Most comments stated that CDRH should allow the use of a "split predicate," but several of these comments seemed to confuse the concepts of "split" and "multiple" predicates: many of the examples cited to support the use of a "split predicate" were actually cases in which "*multiple* predicates" were used, such as multi-parameter monitors. However, other comments clearly understood the distinction between these two concepts and supported the use of a "split predicate."

Example: "Split Predicate"

Thermal blankets are devices that contain sealed channels of cold water, which are wrapped around a patient to reduce core body temperature. An immersion hydrobath is a device that consists of water agitators and that may include a tub to be filled with water. It is used in hydrotherapy to relieve pain and itching and as an aid in the healing process of inflamed and traumatized tissue, and it serves as a setting for removal of contaminated tissue.

A hypothetical 510(k) for a new thermal regulation device is under review. The device uses a circulating cold water bath to reduce a patient's core body temperature.

Although the new device has the same intended use as a thermal blanket (*i.e.*, reducing core body temperature), it has different technological characteristics that could affect safety or effectiveness. Because the new device requires the patient to be in direct contact with cold water, it is associated with additional safety risks, including drowning, infection, electrocution, cardiac arrest, and death.

Although the new device has the same technological characteristics as an immersion hydrobath, these devices have different intended uses.

It has been suggested that, because neither the new device nor its individual functional components meet the criteria for substantial equivalence to the thermal blanket (in and of itself) or the immersion hydrobath (in and of itself), the new device should not be found substantially equivalent to either of these marketed devices.

Due to the limitations of CDRH's data systems (described further in Section 5.2.2.2, below), it is difficult to assess the impact of using more than one predicate. As described above, a submitter may cite more than one predicate in its 510(k) even when the substantial equivalence determination will rely on only one. Similarly, a submitter may bundle many devices into a single submission, with one predicate for each separate device. Without examining every individual 510(k), it is not possible to determine how many predicates were used as the basis of each substantial equivalence determination, and, where more than one predicate was used, whether the determination relied on "multiple predicates" or on a "split predicate." Still, two apparent trends are worthy of note.

As shown in Table 5.4, below, 510(k)s that cite more than one predicate may be more likely to have longer review times: as the number of predicates cited increases, the mean FDA review time increases, and a greater percentage of 510(k)s take more than 90 days to complete. One possible explanation for this apparent trend is that a number of 510(k)s that cite more than one predicate are bundled submissions, which require the separate review of many devices and can therefore be more time-consuming than a non-bundled submission. A second possible explanation is that some 510(k)s that cite more than one predicate are for devices with "multiple predicates" (*i.e.*, multi-functional devices), which tend to be more complex. Multiplex assays, for example, are in vitro diagnostic devices that assay two

or more analytes (targets).[132] 510(k)s for such devices may cite assays for multiple analytes as predicates. In these cases, in addition to reviewing each analyte individually, reviewers must also evaluate the consequences of combining different analytes in a single panel, such as interference or cross-reactivity. 510(k)s for multi-parameter systems may also be complex. In order to adequately address the various scientific issues associated with multiplex or multi-parameter devices, reviewers may need additional review time, including time to consult other experts within or outside of the Center.

Table 5.4. FDA Review Time by Number of Predicates Cited [133]

Number of Predicates Cited	Mean FDA Days	≤30 Days % Completed (#)	31-90 Days % Completed (#)	91-365 Days % Completed (#)	>365 Days % Completed (#)	All % Completed (#)
1	57.2	28.9% (1,814)	64.7% (4,055)	6.3% (393)	0.1% (5)	100% (6,267)
2-5	64.6	21.9% (1,889)	68.9% (5,935)	9.1% (783)	0.1% (6)	100% (8,613)
>5	66.8	23.4% (507)	65.0% (1,410)	11.5% (249)	0.1% (3)	100% (2,169)
Unknown	63.9	26.8% (344)	63.1% (810)	9.7% (124)	0.4% (5)	100% (1,283)
All	62.3	24.8% (4,554)	66.6% (12,210)	8.4% (1,549)	0.1% (19)	100% (18,332)

Table 5.5, below, shows the mean rate of adverse event reports for 510(k)s that cite different numbers of predicates. These data suggest that 510(k)s that cite more than one predicate may be associated with more adverse event reports, on average, than 510(k)s that cite only one. One possible explanation for this apparent trend is that a number of these 510(k)s are bundled submissions comprised of many devices. One would reasonably expect the MDR rates for such submissions to be higher, because they actually represent the sum of MDRs for all of the individual devices that had been bundled together. Another potential explanation for the apparent trend is that some 510(k)s that cite more than one predicate may have been cleared using a "split predicate," and their safety and effectiveness may not have been adequately assessed. It is also possible that 510(k)s that use "multiple predicates" could be complex systems, which, as discussed above, may be associated with additional failure modes because several separate device functions are being combined into a single device. In addition, due to a lack of clarity about CDRH's bundling policy, some reviewers may inappropriately treat 510(k)s for multi-functional systems as bundled submissions and, as a result, review each component in isolation rather

[132] "Multiplex assays," also called "multiplex devices," are usually defined as assays in which two or more targets are assayed through a common process of sample preparation, amplification and/or detection, and interpretation.

[133] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Predicates cited" refers to the predicate(s) and other related submission(s) listed by a submitter in its 510(k). Note that sometimes review staff, in collaboration with the submitter, identify a different predicate(s) for comparison during the 510(k) review process; therefore, the predicate(s) originally cited by the submitter may not be the one(s) on which the substantial equivalence determination is ultimately based. "Unknown" indicates missing data. Values may not sum to 100 percent due to rounding.

than reviewing the device as a single unit.[134] This practice may result in a failure to identify safety or effectiveness issues associated with the use of the system as a whole. It is not possible to confirm or rule out any of these hypotheses without further analysis of this apparent trend in MDR rates.

Table 5.5. Mean MDR Rate per 510(k) by Number of Predicates Cited [135]

Number of Predicates Cited	Total 510(k)s	All MDRs	Death	Injury	Malfunct.
1	6,267	1.75	0.02	0.74	0.93
2-5	8,613	1.78	0.02	0.79	0.93
>5	2,169	5.35	0.05	1.73	3.38
Unknown	1,283	0.43	0.01	0.30	0.13
All	18,332	2.10	0.02	0.85	1.16

- The 510(k) Working Group recommends that CDRH develop guidance on the appropriate use of more than one predicate, explaining when "multiple predicates" may be used. The Center should also explore the possibility of explicitly disallowing the use of "split predicates." In addition, the Center should update its existing bundling guidance to clarify the distinction between multi-parameter or multiplex devices and bundled submissions.

- The 510(k) Working Group recommends that CDRH provide training for reviewers and managers on reviewing 510(k)s that use "multiple predicates," to better assure high-quality review of these often complex devices. This training should clarify the distinction between multi-parameter or multiplex devices and bundled submissions. In addition, CDRH should more carefully assess the impact of submissions for multi-parameter or multiplex devices and bundled submissions on review times, and should consider taking steps to account for the additional complexity of these submissions as it establishes future premarket performance goals.

- The 510(k) Working Group further recommends that CDRH conduct additional analyses to determine the basis for the apparent association between citing more than five predicates and a greater mean rate of adverse event reports.

In addition to the challenges described above, limitations in CDRH's current information technology infrastructure makes it difficult for the Center's staff and external constituencies to access meaningful information about predicate devices. This issue is discussed further in Sections 5.2.2.1 and 5.2.2.2, below.

[134] In the Working Group's Reviewer Survey, 21 percent of respondents in the reviewer cohort and 19 percent of respondents in the manager cohort indicated, incorrectly, that submissions for multi-parameter bedside monitors constituted a "bundled submission" but not a "bundled device" ("system"). *See* Appendix D for a full listing of survey questions and results.

[135] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Predicates cited" refers to the predicate(s) and other related submission(s) listed by a submitter in its 510(k). Note that sometimes review staff, in collaboration with the submitter, identify a different predicate(s) for comparison during the 510(k) review process; therefore, the predicate(s) originally cited by the submitter may not be the one(s) on which the substantial equivalence determination is ultimately based. "Unknown" indicates missing data. "MDR rate" refers to the number of MDRs for a device per 1,000 days on the market. Note that MDRs frequently do not cite the 510(k) number of the device associated with the adverse event; therefore, these data likely underestimate the total number of MDRs per device.

5.1.3. Finding: Although there exists an alternative regulatory pathway for devices that lack a clear predicate but whose risks do not warrant class III controls (*i.e.*, the process for Evaluation of Automatic Class III Designation, also known as the de novo classification process), this pathway, as currently implemented, is inefficient and has not been utilized optimally across the Center.

Recommendation: CDRH should reform its implementation of the de novo classification process to provide a practical, risk-based option that affords an appropriate level of review and regulatory control for eligible devices.

As described in Section 4.3.2.3, above, the de novo classification process was established under FDAMA as a mechanism to allow for classification of devices for which there is no predicate, but whose risks may not warrant a PMA approach. If it is determined through review of relevant evidence that the risks of the new device are such that general controls alone or general and special controls can provide reasonable assurance of safety and effectiveness, the device may be classified into class I or II. If general controls are not sufficient and it is not possible to identify special controls that will mitigate the risks associated with the device, then the device would remain in class III. Any device classified into class I or II through the de novo process may be used as a predicate for future 510(k)s.

Section 513(f)(2) of the FDCA [136]

(A) Any person who submits a report under section 510(k) for a type of device that has not been previously classified under this Act, and that is classified into class III under paragraph [513(f)(1)], may request, within 30 days after receiving written notice of such a classification, [FDA] to classify the device under the criteria set forth in subparagraphs (A) through (C) of subsection [513](a)(1). The person may, in the request, recommend to [FDA] a classification for the device. Any such request shall describe the device and provide detailed information and reasons for the recommended classification.

(B) (i) Not later than 60 days after the date of the submission of the request under subparagraph (A), [FDA] shall by written order classify the device involved. Such classification shall be the initial classification of the device for purposes of paragraph [513(f)(1)] and any device classified under this paragraph shall be a predicate device for determining substantial equivalence under paragraph [513(f)(1)].

(ii) A device that remains in class III under this subparagraph shall be deemed to be adulterated within the meaning of section 501(f)(1)(B) until approved under section 515 or exempted from such approval under section 520(g).

(C) Within 30 days after the issuance of an order classifying a device under this paragraph, [FDA] shall publish a notice in the Federal Register announcing such classification.

The legislative history surrounding FDAMA indicates that the intent of introducing the de novo process was two-fold. First, the process would avoid subjecting lower risk devices to a PMA review, when such a review is not necessary to provide reasonable assurance of safety and effectiveness. Second, the process would help prevent attempts to fit devices into the 510(k) framework that are not suited to a

[136] 21 USC §360c(f)(2).

predicate comparison: it would allow FDA to "avoid time and resources consuming [*sic*] substantial equivalence determinations that rely on *remote* predicates."[137]

Soon after the passage of FDAMA, CDRH issued guidance outlining procedures for de novo classification.[138] The guidance states, "In order to be placed in class I or II under the Evaluation of Automatic Class III Designation provision, a device must first have been reviewed in connection with a 510(k) premarket notification. It is important that this review consider all aspects of the device. If the division identifies questions of safety and effectiveness that suggest additional information is needed, these issues should either be addressed through deficiency letter and responses, or the NSE letter should indicate that these issues have not been resolved."[139] It continues, "The [de novo] review should be based on the information submitted in the request for Evaluation of Automatic Class III Designation as well as information submitted in the 510(k). The division reviewing the request will be responsible for drafting the written order determining the classification of the device as well as a draft federal register notice announcing the classification of a device into class I or class II. These orders should be in the form of a classification action and identify the applicability of design controls and 510(k) notification for class I products and identify the special controls for class II products."[140]

As shown in Figure 5.3, below, the de novo pathway is currently used for only a small number of devices, in part because only a small percentage of devices are found NSE due to lack of a predicate. Figure 5.4, below, shows the average total time from receipt of a 510(k) to approval of a de novo request for that device, including both active FDA review time and time "on hold" while a request for additional information is pending. The combination of a 510(k) review and a de novo review can create a lengthy path to market, making it impractical for many submitters. De novo review times have increased over the past few years, particularly for the Center's Office of Device Evaluation (ODE). According to Center staff, this trend is in part due to the complexity of these submissions, which may involve novel technologies or uses. The Center's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) has tended to take less time than ODE to address de novo devices. This is in part because IVD devices are more homogeneous than non-IVD devices, which range widely in complexity and risk, and because IVD 510(k)s frequently contain clinical data. Therefore, it is easier for OIVD staff to fully evaluate the risks and benefits of these devices up front as part of the 510(k) review process, leaving less to do during the review of the de novo request.

EMBARGOED

[137] S. Rep. No. 105-43, 105th Cong. 1st Sess. (1997), at 36 (emphasis added).

[138] "New Section 513(f)(2) – Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff" (February 19, 1998). Available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf.

[139] *Id.* at 4.

[140] *Id.* at 5.

Figure 5.3. Number of De Novo Requests Received by Office: CY 1998-2009

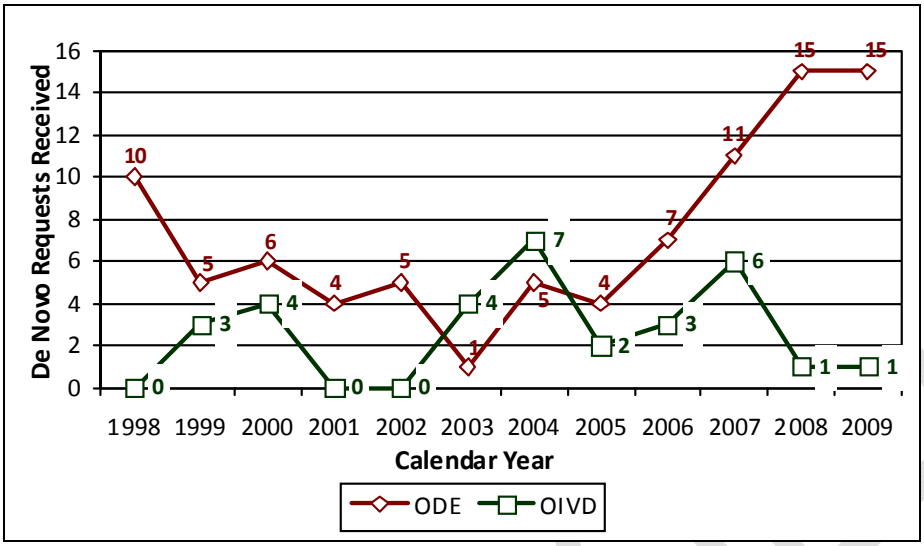
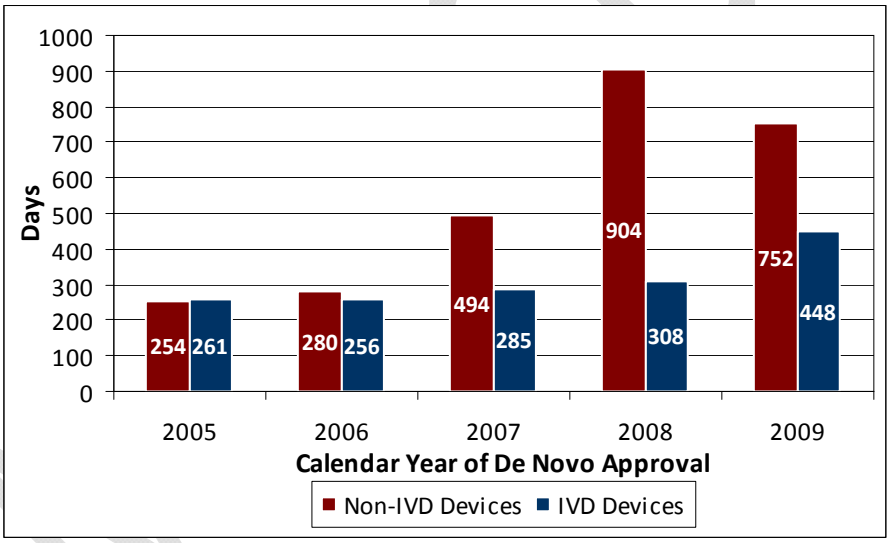


Figure 5.4. Average Total Time from 510(k) Receipt to De Novo Approval: CY 2005-2009 [141]



One factor that may contribute to the longer timeframes for de novo classification is that CDRH conducts a full 510(k) review prior to initiating the de novo process. As described above, the Center's de novo guidance suggests that reviewers should "consider all aspects of the device," and potentially undertake multiple review cycles. However, in certain situations in which it is clear that a device has a new intended use or different technological characteristics that raise different questions of safety and effectiveness, it may not be an efficient use of resources to continue a 510(k) review at length. It may be more efficient for the Center to issue an NSE decision quickly and communicate clearly and early on with the submitter about what additional information it would need to include in a de novo request, should it choose to submit such a request, in order to provide the Center with a sufficient understanding of the new device's risks and benefits.

[141] "Average Total Time" includes both active FDA days and days "on hold" while a request for additional information is pending.

In some cases, particularly for devices that employ a novel technology or a novel use of an existing technology that is not yet well-understood, clinical information may be necessary to support a de novo classification determination. As described further in Section 5.2.1.3, below, although such information is routinely included in 510(k)s for in vitro diagnostic devices, it is often not included in 510(k)s for non–in-vitro-diagnostic devices. It would be beneficial for CDRH to communicate the need for clinical information for a given de novo eligible device as early as feasible, in order to avoid the need for major mid-course corrections and unexpected delays. Depending on the technology involved, clinical information needed to support a de novo request may not be as extensive as the formal clinical trial data required to support a PMA; however, some clinical evidence may be necessary to address any otherwise unanswered questions of safety and effectiveness presented by certain devices. For other devices, clinical information may not be necessary for a de novo review. In some cases, a device should have been reviewed under the de novo classification process, but CDRH kept it as a 510(k) and requested clinical data as part of the 510(k) review to address questions of safety or effectiveness. By requesting additional information during the 510(k) review, CDRH reached an appropriate decision; however, it did so in a nontransparent, less timely, and less predictable manner. Such an approach has created further uncertainty with respect to 510(k) review requirements and timeframes.

Another factor that contributes to lengthy de novo review times is that, to date, CDRH has typically developed device-specific guidance to serve as special controls for each device classified into class II through the de novo process, and has issued such guidance with each de novo classification order. According to staff, particularly in ODE, this practice can be very time-consuming. There may be other types of special controls that the Center should consider in lieu of guidance. Section 513(a)(1)(B) of the FDCA provides for several types of potential special controls, "including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as [FDA] deems necessary…."

Instead of relying nearly exclusively on device-specific guidance documents as special controls, it may be possible for CDRH to develop, through a combination of guidance and regulation, a single generic set of controls that could serve as baseline special controls for devices classified into class II through the de novo process, and to which further device-specific special controls could be added as needed.

- The 510(k) Working Group recommends that CDRH revise existing guidance to streamline the current implementation of the de novo classification process and clarify its evidentiary expectations for de novo requests. The Center should encourage pre-submission engagement between submitters and review staff to discuss the appropriate information to provide to CDRH for devices eligible for de novo classification, potentially in lieu of an exhaustive 510(k) review. The Center should also consider exploring the possibility of establishing, as described above, a generic set of controls that could serve as baseline special controls for devices classified into class II through the de novo process, and which could be augmented with additional device-specific special controls as needed.

5.2. Well-Informed Decision Making

In order to fulfill the goals of the 510(k) program, the statutory framework must be implemented and administered in a manner that both supports fully informed decision making and provides predictability. CDRH staff must have access to a sufficient level of information about 510(k) devices, as well as tools

that allow for the optimal use of that information. To obtain such information without creating unnecessary delays and burden, CDRH must provide submitters with as much up-front clarity as feasible about its evidentiary expectations. There are several steps CDRH could take to reduce uncertainty and unpredictability in the 510(k) process for both Center staff and submitters.

5.2.1. Finding: It is challenging for CDRH to obtain, in an efficient and predictable manner, the information it needs to make well-supported premarket decisions and assure that each new or modified 510(k) device is substantially equivalent to a valid predicate.

Recommendation: CDRH should take steps through guidance and regulation to facilitate the efficient submission of high-quality 510(k) device information, in part by better clarifying and more effectively communicating its evidentiary expectations through the creation, via guidance, of a new "class IIb" device subset.

In order for CDRH to make well-informed regulatory decisions, the Center must have an adequate understanding of 510(k) devices, based on up-to-date, clearly presented device information and a sufficient type of and level of evidence on safety and effectiveness.

5.2.1.1. Unreported Device Modifications

Under current FDA regulations, a manufacturer is not required to submit a new 510(k) for a device modification unless the modification "could significantly affect the safety or effectiveness of the device" or there has been a "major change or modification to the intended use of the device."[142] These regulations allow manufacturers to make incremental or so-called "minor" modifications to devices on the market that are immaterial to safety and effectiveness, without undue regulatory burden. However, because CDRH is only notified of certain device changes, the Center does not always have complete information about the current functions and features of devices on the market. In some situations, a manufacturer may make several successive minor modifications, none of which would warrant a new 510(k) individually, but which, taken together, could significantly affect safety and/or effectiveness.

When a 510(k) *is* submitted for a particular modification, CDRH must evaluate not only the effect of that modification itself on the device's safety and effectiveness, but also the cumulative effect of any unreported modifications that preceded it. Submitters do not always initially provide sufficient information to make such an evaluation, and, although CDRH has recommended in guidance that submitters list the modifications made to the device since the last clearance,[143] there is no explicit requirement for them to do so. This can create challenges for review staff and may necessitate requests for additional information in the midst of a review, leading to delays. It can be particularly problematic when a submitter attempts to use the Special 510(k) pathway — which, as described in Section 4.3.3.1, above, does not require the submission of performance data — for a modification that is ineligible for a Special 510(k) (*i.e.*, one that may affect intended use or that alters the fundamental scientific technology of the device). Table 5.6, below, shows that devices cleared through the Special 510(k) pathway appear to have a higher rate of MDRs than devices cleared through other mechanisms. This apparent trend may reflect misuse of the Special 510(k) option to review modifications that should have been reviewed more thoroughly in a traditional 510(k); however, additional analysis is necessary.

[142] 21 CFR 807.81(a)(3). Note that, as discussed in Section 5.1.1.1 of this report, the use of the term "intended use" here is inconsistent with the use of this term in the statute and the 510(k) flowchart.

[143] *See* "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)."

Table 5.6. Mean MDR Rate per 510(k) by Submission Type [144]

Submission Type	Total 510(k)s	All MDRs	Death	Injury	Malfunct.
Traditional	13,973	1.98	0.018	0.77	1.140
Special	3,612	2.80	0.043	1.25	1.403
Abbreviated	747	0.76	0.009	0.35	0.392
All	18,332	2.10	0.022	0.85	1.161

Further, manufacturers do not always submit new 510(k)s for modifications that warrant them. 21 CFR 807.81(a)(3) states that a new 510(k) should be submitted for modifications, including changes in "design, material, chemical composition, energy source, or manufacturing process" that "*could* significantly affect the safety or effectiveness of the device" (emphasis added), *i.e.*, changes that have the *potential* to significantly affect safety and/or effectiveness. Although CDRH has issued guidance to help 510(k) holders determine when to submit a new 510(k) for a change in an existing device,[145] there is concern that manufacturers misinterpret the regulation to mean that a new 510(k) is only necessary if a modification definitively *does* affect safety and/or effectiveness. There is also concern that manufacturers misinterpret the regulation to mean that a new 510(k) is only necessary if a modification could *negatively* affect safety and/or effectiveness. In actuality, a new 510(k) is also required for changes that potentially could have a positive effect, because what was expected to have a positive impact may in fact create new risks that would not be detected without an adequate assessment. In addition, the guidance[146] does not specifically address what types of manufacturing process changes might warrant the submission of a new 510(k). For these reasons, significant modifications may be made without an adequate level of regulatory oversight.

Case Study: Unreported Modifications

Background. A muscle stimulator is a class II device that repeatedly contracts muscles by passing electrical currents through electrodes contacting the affected body area. A transcutaneous electrical nerve stimulator for pain relief is a class II device used to apply an electrical current to electrodes on a patient's skin to relieve pain.

Issue. A device was cleared as a muscle stimulator with indications for use that included relaxation of muscle spasms and increased local blood circulation. The device was also cleared as a transcutaneous electrical nerve stimulator for over-the-counter temporary relief of lower back pain.

After clearance, CDRH found that the manufacturer's informational materials stated that the device had several additional indications for use, including treatment of anemia, headaches, arthritis, hyper-mobility syndrome, plantar fasciitis, insomnia, chronic pain, stiff neck, fatigue, and tendonitis, among others. The addition of these indications for use constitutes a modification that changes the intended use of the device and that has the potential to affect both safety and effectiveness. Such a change should have resulted in a new premarket submission. A Warning Letter was issued to the

[144] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's methods for data collection and analysis. "MDR rate" refers to the number of MDRs for a device per 1,000 days on the market. Note that MDRs frequently do not cite the 510(k) number of the device associated with the adverse event; therefore, these data likely underestimate the total number of MDRs per device.

[145] "Deciding When to Submit a 510(k) for a Change to an Existing Device."

[146] *Id.*

manufacturer.

***Impact*.** Because this modification was not reported to CDRH, the device was marketed to patients without an appropriate assessment of whether or not it was substantially equivalent to a predicate or safe and effective for its intended use.

- The 510(k) Working Group recommends that CDRH revise existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).

- The 510(k) Working Group further recommends that CDRH explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k), and clearly explaining why each modification noted did not warrant a new 510(k). The Center could consider phasing in this requirement, applying it initially to the "class IIb" device subset described in Section 5.2.1.3, below, for example, and expanding it to a larger set of devices over time.

5.2.1.2. Quality of Submissions

In order for CDRH review staff to efficiently and accurately evaluate 510(k) devices, it is important for 510(k) submissions to be clear and complete.

Lack of Clarity. If a 510(k) submission is not sufficiently clear, it can be difficult for review staff to efficiently identify the critical features of a new device and the relevant points of comparison to the predicate.

21 CFR 807.87 describes the information required in a 510(k). It states that a 510(k) must include "[p]roposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use. Where applicable, photographs or engineering drawings should be supplied."[147] A 510(k) must also contain a "statement indicating the device is similar to and/or different from other products of comparable type in commercial distribution, accompanied by data to support the statement. This information may include identification of similar products, materials, design considerations, energy expected to be used or delivered by the device, and a description of the operational principles of the device."[148]

CDRH has issued guidance that elaborates upon these regulations, recommending a standard 510(k) format with several sections including, but not limited to, "Device Description," "Substantial Equivalence Discussion," "Proposed Labeling," and "Performance Testing."[149] With respect to the "Device Description" section, the guidance states:

> We recommend that you describe the performance specifications and include a brief description of the device design requirements in this section. We also recommend that you identify all models, as well as all accessories or components, included in the submission. If diagrams, dimensions, tolerances, and/or schematics are useful to fully

[147] 21 CFR 807.87(e).
[148] 21 CFR 807.87(f).
[149] "Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s" (August 12, 2005). Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm.

> describe and characterize the device, we recommend that you include them for each device, accessory or component included in the 510(k) submission. We also recommend that you provide a list of all patient contacting components and their respective materials.[150]

With respect to the "Substantial Equivalence Discussion" section, the guidance states, "We recommend that you provide a detailed comparison between your device and the predicate sufficient to demonstrate the substantial equivalence of the devices, as applicable, in terms of: indications for use; technology; and performance specifications, including any testing."[151]

CDRH review staff report that, despite this guidance, the quality and clarity of 510(k)s vary. Staff state that the information contained in the "Device Description" section of a 510(k) is often a general summary, and it frequently does not provide an adequate level of detail about the new device. Staff report that important information that should be identified in this section is often spread out in other sections of the 510(k), including the sections designated for the submitter's substantial equivalence discussion, proposed labeling, and performance testing. Review staff have also found that, for many 510(k)s, information provided in one section is inconsistent with information provided in another. It can therefore be difficult for reviewers to readily develop a meaningful understanding of the device's core design and functions. In addition, some submissions include in the "Substantial Equivalence Discussion" section a list of several potential predicates with little to no explanation of the relevant points of comparison between each predicate and the new device. Further, as described above, although CDRH has recommended in guidance[152] that submitters list in each new 510(k) previous "minor" modifications to their devices that did not warrant a 510(k), submitters are not required to do so.

Without sufficient clarity, it can be needlessly time-consuming and labor-intensive for CDRH review staff to identify all of the critical information in a 510(k). Poor quality 510(k)s can result in additional information requests and multiple review cycles that otherwise could have been avoided. In some situations, as illustrated in the example below, key information may be inadvertently overlooked.

Example: Lack of Clarity

A 510(k) is submitted for modifications to a marketed device. The 510(k) states that the device modifications are technical in nature, and that the physician's user manual has also been updated to reflect these technical changes. The submitter provides a redlined version of the user manual, highlighting the changes to the instructions for use that corresponded to the device modifications. The FDA reviewer reviews the device modifications that the submitter has outlined and clears the 510(k).

Another 510(k) is submitted for a subsequent modification to the same device. The reviewer notices that the device labeling includes a claim that the device can be used for prescription home use. This claim is not included in the Indications for Use statement. In this case, clinical data are required to support a home use indication.

When questioned regarding this change, the submitter states that the home use indication was cleared in the previous 510(k). Upon further examination, the reviewer determines that the home use indication had been included in the previous 510(k), albeit not in the "Indications For Use"

[150] *Id.* at 8.
[151] *Id.* at 9.
[152] "Deciding When to Submit a 510(k) for a Change to an Existing Device."

statement, and not as one of the redlined user manual changes. It had been overlooked and not adequately reviewed.

- The 510(k) Working Group recommends that CDRH consider adopting the use of an "assurance case" framework for 510(k) submissions. An "assurance case" is a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence. It is a way to structure arguments to help ensure that top-level claims are credible and supported.[153] If CDRH pursues this approach, the Center should develop guidance on how submitters should develop and use an assurance case to make adequate, structured, and well-supported predicate comparisons in their 510(k)s. The guidance should include the expectation that all device description and intended use information should be submitted and described in detail in a single section of a 510(k). The guidance should also clearly reiterate the long-standing expectation that 510(k)s should describe any modifications made to a device since its previous clearance. CDRH should also develop training for reviewers and managers on how to evaluate assurance cases.

- The 510(k) Working Group further recommends that CDRH explore the possibility of requiring each 510(k) submitter to provide as part of its 510(k) detailed photographs and schematics of the device under review, in order allow review staff to develop a better understanding of the device's key features. Currently, CDRH receives photographs *or* schematics as part of most 510(k)s; however, receiving both as a general matter would provide review staff with more thorough information without significant additional burden to submitters. Further, CDRH could include photographs and schematics, to the extent that they do not contain proprietary information, as part of its enhanced public 510(k) database, described in Section 5.2.2.2, below, to allow prospective 510(k) submitters to develop a more accurate understanding of potential predicates. Exceptions could be made for cases in which a photograph or schematic of the device under review will not provide additional useful information, as in the case of software-only devices. CDRH should also explore the possibility of requiring each 510(k) submitter to keep at least one unit of the device under review available for

[153] The three main elements of an assurance case are: (1) the claim, a statement about a property of the system or some subsystem; (2) the evidence, information that demonstrates the validity of the claim; and (3) the argument, a statement that links the evidence to the claim, by describing what is being proved or established (*i.e.*, the claim), identifying the relevant pieces of evidence, and providing reasoning that the evidence is adequate to support the claim. In an assurance case, many arguments, with their supporting evidence, may be grouped under one top-level claim. Arguments may also introduce sub-claims or assumptions which require further exposition. For a complex case, there may be a complex web of arguments and sub-claims. Because the assurance case structure requires each claim to be clearly supported by corresponding evidence, adopting such a structure for 510(k)s would help assure that submitters provide clear and adequate evidence, as needed, to support a determination of substantial equivalence to a predicate. By better assuring the clarity and completeness of information initially provided in 510(k) submissions, the assurance case could help alleviate the need for substantial follow-up questions and multiple rounds of review. Although assurance cases have not generally been used to date in the premarket review of medical devices, they have been used in other industries with safety-critical systems (*e.g.*, the nuclear and avionics industries). As part of its recent *Infusion Pump Improvement Initiative*, FDA issued guidance on infusion pumps, recommending that infusion pump manufacturers submit their 510(k)s using the assurance case framework. *See* "Guidance for Industry and FDA Staff – Total Product Life Cycle: Infusion Pump – Premarket Notification [510(k)] Submissions," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm206153.htm#6. For more information about assurance cases, *see*, *e.g.*: Graydon P, Knight J, and Strunk E, "Assurance Based Development of CriticalSystems," Proc. of 37th Annual International Conference on Dependable Systems and Networks, Edinburgh, U.K., 2007; Kelly T, "Arguing Safety – A Systematic Approach to Managing Safety Cases," Ph.D. Dissertation, University of York, U.K., 1998; Kelly T, "Reviewing Assurance Arguments – A Step-by-Step Approach," Proc. of Workshop on Assurance Cases for Security – The Metrics Challenge, Dependable Systems and Networks, July 2007; Kelly T and McDermid J, "Safety Case Patterns – Reusing Successful Arguments," Proc. of IEE Colloquium on Understanding Patters and Their Application to System Engineering, London, Apr. 1998; Weinstock CB and Goodenough JB, "Towards an Assurance Case Practice for Medical Devices," Carnegie Mellon Software Engineering Institute, October 2009.

CDRH to access upon request, so that review staff could, as needed, examine the device hands-on as part of the review of the device itself, or during future reviews in which the device in question is cited as a predicate.

Improper Use of Recognized Standards. Section 514(c)(1) of the FDCA[154] describes the possibility of using, as part of a 510(k) submission, consensus standards that have been entirely or partially recognized by FDA. This section states, "[FDA] shall, by publication in the Federal Register, recognize all or part of an appropriate standard established by a nationally or internationally recognized standard development organization for which a person may submit a declaration of conformity in order to meet a premarket submission requirement or other requirement under this Act to which such standard is applicable."

Standards can be a useful resource for industry and FDA staff. The appropriate use of standards can help streamline and increase consistency in the premarket review process by providing a consensus approach to certain aspects of the evaluation of device safety and effectiveness, such as testing methods or pass/fail performance criteria. However, the 510(k) Working Group found that, due to insufficient guidance and training, not all CDRH review staff and submitters have an accurate understanding of how to properly use standards in 510(k) submissions. If done improperly, the use of standards may fail to provide meaningful or sufficient information about a device under review.

First, it is important for review staff to recognize that the use of recognized consensus standards is generally only one part of a premarket submission. A specific device may raise safety and/or effectiveness questions not addressed by any recognized consensus standard, or a specific FDA regulation may require additional information beyond what the recognized consensus standard provides. Even when an application appropriately demonstrates conformity with one or more standards, a reviewer should evaluate the totality of the submission to assure that it contains all necessary information.

Second, submitters do not always use recognized standards appropriately. For example, a submitter may not use the most current version of a standard, or it may not realize that only certain aspects — not all — of a particular standard have been recognized by FDA. In addition, submitters sometimes attempt to use standards that do not apply to a particular type of device or testing. When submitters do not use standards appropriately, it may be necessary for review staff to request additional information, leading to delays.

Third, submitters do not always document their use of standards properly. Often submitters do not indicate how they used a given standard and how they deviated from that standard.[155] Failure to acknowledge deviations from a standard can create confusion when review staff compare the information provided in a 510(k) to the standard itself. Similarly, submitters do not always use "declarations of conformity" to recognized consensus standards appropriately.[156] Some submitters, for example, have attempted to declare conformity to a testing method standard without also providing the results from the associated test for review. Other submitters have included declarations of conformity to a standard in their 510(k)s indicating that they *will* conduct testing in conformity with the standard,

[154] 21 USC §360d(c)(1).

[155] Submitters are supposed to provide such information on FDA Form 3654.

[156] Declarations of Conformity to Recognized Consensus Standards are described in "Guidance for Industry and FDA Staff: Recognition and Use of Consensus Standards." Available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077274.htm.

but without actually having conducted it. This inappropriate use of standards does not provide CDRH review staff with meaningful information about the safety and effectiveness of the device under review and how it compares to the predicate.

- The 510(k) Working Group recommends that CDRH provide additional guidance and training for submitters and review staff regarding the appropriate use of consensus standards, including proper documentation within a 510(k). CDRH should also consider revising the requirements for "declaration of conformity" with a standard, for example by requiring submitters to provide a summary of testing to demonstrate conformity if they choose to make use of a "declaration of conformity."

Incomplete Information. It may be necessary for a submitter to include clinical or other scientific information in its 510(k) to support a finding that the device under review is as safe and effective as the predicate and does not raise different questions of safety and effectiveness when compared to the predicate. Under FDA's PMA regulations, each application is explicitly required to contain a summary of all information known or that should be reasonably known to the applicant concerning the safety and/or effectiveness of the device under review.[157] Current regulations do not expressly state that such a summary must be included in each 510(k); instead, 510(k) submitters are required to provide "data to support the statement" regarding substantial equivalence.[158] Consequently, important information that is relevant to FDA's review may not be included in a 510(k) upon initial submission, even when that information is readily available to the submitter.

Example: Incomplete Information

A submitter includes as part of its 510(k) three studies supporting the proposition that a particular marker is associated with a risk of coronary heart disease (CHD). Unbeknownst to CDRH, the submitter failed to include three other equally powered studies that do not support the association.

If CDRH review staff do not initially have sufficient information to make a well-supported review decision, they may need to seek additional information from the submitter, leading to delays for both the Center and industry. If staff had a summary of all available safety and effectiveness information up front as part of the initial 510(k) submission, it could allow them to complete the review more efficiently. Instead of needing to issue formal and time-consuming deficiency letters to obtain safety and effectiveness data that are available to the submitter, CDRH could simply indicate, as part of an interactive review, the summary items for which it would like a greater level of detail. In addition, providing a summary of relevant information should not present a significant additional burden for 510(k) submitters. Industry representatives have acknowledged in discussions with CDRH that they typically collect such information as part of their own product development processes as part of good business practices.

[157] 21 CFR 814.20(b)(8), states that PMAs must include, among other requirements: (1) "A bibliography of all published reports…, whether adverse or supportive, known to or that should be reasonably known to the applicant and that concern the safety and effectiveness of the device," (2) "An identification, discussion, and analysis of any other data, information, or report relevant to an evaluation of safety or effectiveness of the device known to or that should reasonably be known to the applicant from any source, foreign or domestic, including information derived from investigations other than those proposed in the application and from commercial marketing experience," and (3) "Copies of such published reports or unpublished information in the possession of or reasonably obtainable by the applicant if an FDA advisory committee or FDA requests."

[158] 21 CFR 807.87(f).

- The 510(k) Working Group recommends that CDRH consider revising 21 CFR 807.87, to explicitly require 510(k) submitters to provide a list and brief description of all scientific information regarding the safety and/or effectiveness of a new device known to or that should be reasonably known to the submitter. The Center could then focus on the listed scientific information that would assist it in resolving particular issues relevant to the 510(k) review.

5.2.1.3. Type and Level of Evidence Needed

According to the statutory definition of "substantial equivalence," if a new device has different technological characteristics than the predicate, the 510(k) must contain "information, including appropriate clinical or scientific data if deemed necessary by [FDA], that demonstrates that the device is as safe and effective as a legally marketed device."[159]

While FDA regulations describe the evidence that should be contained in a 510(k), they do so only in broad terms. 21 CFR 807.87(f) states that a 510(k) must include data supporting a statement "indicating the device is similar to and/or different from other products of comparable type in commercial distribution," and such data may include "an identification of similar products, materials, design considerations, energy expected to be used or delivered by the device, and a description of the operational principles of the device." In addition, according to 21 CFR 807.87(g), if a device "has undergone a significant change or modification that could significantly affect the safety or effectiveness of the device, or the device is to be marketed for a new or different indication for use, the premarket notification submission must include appropriate supporting data to show that the manufacturer has considered what consequences and effects the change or modification or new use might have on the safety and effectiveness of the device." Finally, 21 CFR 807.87(l) states that the applicant must provide "[a]ny additional information regarding the device requested by [FDA] that is necessary for [FDA] to make a finding as to whether or not the device is substantially equivalent to a device in commercial distribution."

When a new device has the same intended use with the same indications for use as the predicate, and has the same technological characteristics as the predicate, the evidence needed to support a substantial equivalence determination is generally limited and straightforward. For a few devices that are identical to a predicate (*e.g.*, when a company submits a new 510(k) in order to distribute a pre-existing device), there is no need for performance testing to support a 510(k) clearance. However, most new devices involve different indications for use and/or different technological characteristics than the predicate, and therefore FDA may need data to show that any differences have not altered the intended use or significantly affected the safety and/or effectiveness of the device. Because 510(k) devices vary widely in technological complexity and risk, data requirements for different submissions, appropriately, are not uniform. Submissions may require bench, animal, or clinical data, or a combination thereof.

To provide additional detail about its evidentiary expectations for specific device types, CDRH has issued numerous device-specific guidance documents. The data in Table 5.7, below, suggest that 510(k)s for devices with available device-specific guidance tend to be reviewed more efficiently than those without such guidance. However, 63 percent of the 510(k)s in the Working Group's data set lack device-specific guidance.[160]

[159] Section 513(i)(1)(A)(ii)(I) of the FDCA (21 USC §360c(i)(1)(A)(ii)(I).

[160] *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis.

Table 5.7. FDA Review Time by Availability of Guidance [161]

Guidance Available	Mean FDA Days (Mean Total Days)	≤30 Days % Completed (#)	31-90 Days % Completed (#)	91-365 Days % Completed (#)	>365 Days % Completed (#)	All % Completed (#)
Yes	57.2 (93.0)	28.7% (1,937)	65.5% (4,424)	5.7% (387)	0.0% (3)	100% (6,751)
No	65.2 (139.5)	22.6% (2,617)	67.2% (7,786)	10.0% (1,162)	0.1% (16)	100% (11,581)
All	62.3 (122.4)	24.8% (4,554)	66.6% (12,210)	8.4% (1,549)	0.1% (19)	100% (18,332)

As described in Section 4.4, above, the average number of 510(k) review cycles and the number of withdrawn or deleted 510(k)s have been growing steadily over the past several years.[162] These trends suggest that there is insufficient clarity about what evidence should be included in a 510(k) submission, as well as insufficient clarity in 510(k) submissions themselves (as discussed above), and that this lack of clarity is becoming increasingly problematic for both the Center and industry. On the one hand, review staff have found it challenging to efficiently obtain the evidence necessary to compare a new device to its predicate and to address any additional safety and/or effectiveness concerns presented by the new device. On the other hand, submitters have found the 510(k) pathway to be less and less predictable, and they report that this lack of predictability may be hindering device development and innovation. In some cases, sponsors have argued that the evidence the Center has requested is not relevant to a 510(k) review.

The 510(k) Working Group identified several steps CDRH could take to allow review staff to obtain sufficient evidence from submitters in a more predictable and efficient manner. The preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making discusses the importance of improving the guidance development process and making use of other tools to communicate the Center's current thinking and evidentiary expectations both within the 510(k) context and in other areas of regulatory decision making. Therefore, the following subsections focus on issues that are unique to the 510(k) program.

Most 510(k) submissions include some combination of bench and animal data. However, a key challenge in the 510(k) program for both review staff and submitters is a lack of clarity about when other types of information may be necessary to support a substantial equivalence determination, including clinical data and manufacturing information. Further, as discussed in Section 5.3.1.1, below, a lack of familiarity with particular device types or technologies among CDRH review staff may influence the Center's data requests.

Given the heterogeneity of devices that CDRH oversees, it is not feasible to definitively identify all data needs for all situations; some data requirements need to be determined on a case-by-case basis. However, it may be possible for CDRH to provide, at least as a heuristic, more up-front clarity for staff

[161] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. Values may not sum to 100 percent due to rounding.

[162] *See* Figures 4.8 and 4.9.

and submitters about specific device types that are most likely to be associated with special data needs. Both Center staff and members of industry have expressed support for such an approach.

- The 510(k) Working Group recommends that CDRH develop guidance defining a subset of class II devices, called "class IIb" devices, for which clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting, would *typically* be necessary to support a substantial equivalence determination. Delineating between "class IIa" and "class IIb" would not reconfigure the current, three-tiered device classification system established by statute; it would represent only an administrative distinction. The development of a "class IIb" guidance would provide greater clarity regarding what submitters would generally be expected to provide for certain 510(k)s. Determining what device types might be included in "class IIb" would require further consideration. Potential candidates may include some implantable, life-sustaining devices, and/or life-supporting devices, which present greater risks than other class II device types. A specific type of device may be removed from the "class IIb" subset as its technology and its risk/benefit profile in clinical practice become better understood. The types of evidence that could be required for "class IIb" devices are discussed in greater detail in the following subsections. As part of its guidance, CDRH should make clear that the delineation between "class IIa" and "class IIb" is meant to be a general guideline only. The types of evidence described below may at times be required for a device that was previously in "class IIa" but for which the Center has changed its evidentiary expectations on the basis of new scientific information, as described in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making. In addition, such evidence may be required for a device that has not yet been specifically identified as a "class IIa" or "class IIb" device. For example, in some situations, a new device may be developed whose technology or use may be so new that it is not possible for CDRH to determine whether it should be included in "class IIa" or "class IIb" until it meets with the submitter to obtain more information. Further, it is possible that not all devices within the "class IIb" subset would necessarily require *all* of the types of evidence described below; therefore, the guidance should advise manufacturers of "class IIb" devices to engage with the Center to discuss the type of evidence appropriate for their devices.

- The 510(k) Working Group further recommends that CDRH develop and implement training for review staff and industry regarding the delineation between "class IIa" and "class IIb."

Clinical Information. Because clinical studies can be time- and resource-intensive, it is important to provide as much predictability as possible about when clinical data[163] may be needed as part of a 510(k), and what type of study should be conducted to provide it, since the type of clinical data necessary will depend on the type of device, what is already known about the device, and what question(s) need to be addressed.

When the 510(k) program was initially developed, many class II devices were well-understood, and basic descriptive information and bench testing of device function were frequently considered sufficient evidence to support device clearance. Over the past thirty years, however, 510(k) devices have become more technologically complex, and many are higher-risk. Some innovations in device design raise questions of safety and effectiveness that can only be answered with clinical data. For example, when a modification to a device is novel, the potential impact of the change on the device's safety and/or effectiveness may not be known or well-understood, and a clinical investigation may therefore be necessary to demonstrate that the device is as safe and effective as the predicate. In other cases, the

[163] The term "clinical data" has not been defined through regulation or internal policy; therefore there is not a consistent understanding within the Center regarding what type of information constitutes "clinical data."

effect of a technological difference between a new device and its predicate is well-understood, and clinical information may be necessary as a special control to mitigate a known risk. For example, a poorly designed user interface on an infusion pump may contribute to user errors that could put patients at risk. This risk can be mitigated if manufacturers conduct usability studies for new or modified pumps, in which the intended users use the pump in the intended use environment, in order to determine whether or not the device has been adequately designed to minimize user error.[164]

The majority of 510(k)s for in vitro diagnostic devices contain some type of clinical information;[165] however, only approximately eight percent of 510(k)s for non–in-vitro-diagnostic devices contain clinical data, and only 11 percent of these 510(k)s reference a predicate for which clinical data was provided. Less than one percent of non–in-vitro-diagnostic 510(k)s reference a clinical trial conducted under an approved Investigational Device Exemption application (IDE).

In the absence of device-specific guidance or special controls, manufacturers lack clear guidance as to when clinical information will be requested, and they may not learn of the need to conduct a study until after they have submitted their 510(k) for review. This can create significant delays. In other cases, a manufacturer may not fully appreciate the effect the differences between its new device and the predicate may have on safety and effectiveness and, therefore, may not have conducted appropriate clinical studies. What may appear as slight differences in performance claims, device design, or other aspects of the device may dramatically affect FDA's thinking regarding the level of evidence necessary to support a substantial equivalence finding. In addition, industry is not always aware of additional information available to FDA or how that information may affect the agency's evidentiary expectations.

Further, when clinical information is necessary, it is important that submitters understand what type and level of clinical evidence should be provided. When FDA requires clinical information, it relies on "valid scientific evidence," which is defined as follows:

> Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.[166]

This definition is notably broad: it encompasses many different types of evidence that may vary in quality, and, although it discusses various *kinds* of evidence, it does not provide insight into the *level* of

[164] CDRH recently announced its *Infusion Pump Improvement Initiative*, a multi-pronged effort to enhance the safety of external infusion pumps by fostering improvements in device design. As part of this initiative, CDRH intends to establish new requirements for infusion pump manufacturers, including a requirement that usability testing be conducted to support premarket clearance of new or modified external infusion pumps. Additional information on the initiative is available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/ucm202501.htm.

[165] Nearly all 510(k)s for in vitro diagnostic devices include information obtained by analyzing clinical samples.

[166] 21 CFR 860.7(c)(2).

evidence that may be necessary to justify a decision. According to CDRH staff, submitters sometimes cite the definition of "valid scientific evidence" together with the "least burdensome" provisions of the FDCA, claiming that it is sufficient for them to provide any type or level of evidence that meets the definition of "valid scientific evidence" with the lowest possible level of burden, even if such evidence fails to provide adequate information on device safety and effectiveness. If a submitter does not engage with CDRH prior to conducting a clinical study, it may not have a clear understanding of what type of clinical data will provide the Center with adequate information to support a substantial equivalence determination.

CDRH recognizes that it should only request clinical data relevant to the 510(k) review, that its requests should be well-informed, including the use of appropriate experts, and that its requests should be made consistently, unless new information has emerged that warrants a change in practice or the Center determines that it previously erred.

- The 510(k) Working Group recommends that CDRH, as part of the "class IIb" guidance described above, provide greater clarity regarding the circumstances in which it will request clinical data in support of a 510(k), and what type and level of clinical data are adequate to support clearance. CDRH should, within this guidance or through regulation, define the term "clinical data" to foster a common understanding among review staff and submitters about types of information that may constitute "clinical data." General recommendations related to the least burdensome provisions, premarket data quality, clinical study design, and CDRH's mechanisms for pre-submission interactions, including the pre-IDE and IDE processes, are discussed further in the preliminary report of the Center's Task Force on the Utilization of Science in Regulatory Decision Making. That report also recommends steps CDRH should take to make well-informed, consistent decisions, including steps to make better use of external experts.

Postmarket Information. For certain devices, including novel and/or particularly complex technologies, it may not be feasible to conduct a large-scale clinical trial prior to clearance. It may therefore be necessary to collect additional data after clearance in order to better evaluate the safety and effectiveness of a device over a longer time period, or in a wider patient population, than would be possible in a premarket clinical study. However, although CDRH has the authority to require postmarket surveillance studies (also called Section 522 studies) as a condition of premarket approval or clearance for PMA devices and certain 510(k) devices that are expected to have significant use in pediatric populations, there is no explicit authority for CDRH to order Section 522 studies as a condition of premarket clearance in other situations.[167] Public comments noted that, if CDRH were to consider pursuing greater authority in this area, such studies should be ordered only in limited circumstances in which there are no other means of collecting such information, and that the rationale for ordering such studies should be clearly defined.

In addition, there has been much discussion about making more use of postmarket information to support clearance of later-generation devices. For example, it may eventually be possible to use "real-world" clinical data in lieu of formal clinical study results to support a 510(k) for a modification to a device. A prerequisite for this consideration, however, is the widespread adoption of a unique device identification (UDI) system, which would make it possible to link information about a particular device with information about a patient's experience with that device. CDRH is currently working to create a UDI system as part of its FY 2010 Strategic Priorities.

[167] Section 522(a)(1)(B) of the FDCA (21 USC §360(a)(1)(B)).

- The 510(k) Working Group recommends that CDRH explore greater use of its postmarket authorities, and potentially seek greater authorities to require postmarket surveillance studies as a condition of clearance for certain devices. If CDRH were to obtain broader authority to require condition-of-clearance studies, the Center should develop guidance identifying the circumstances under which such studies might be appropriate, and should include a discussion of such studies as part of its "class IIb" guidance.

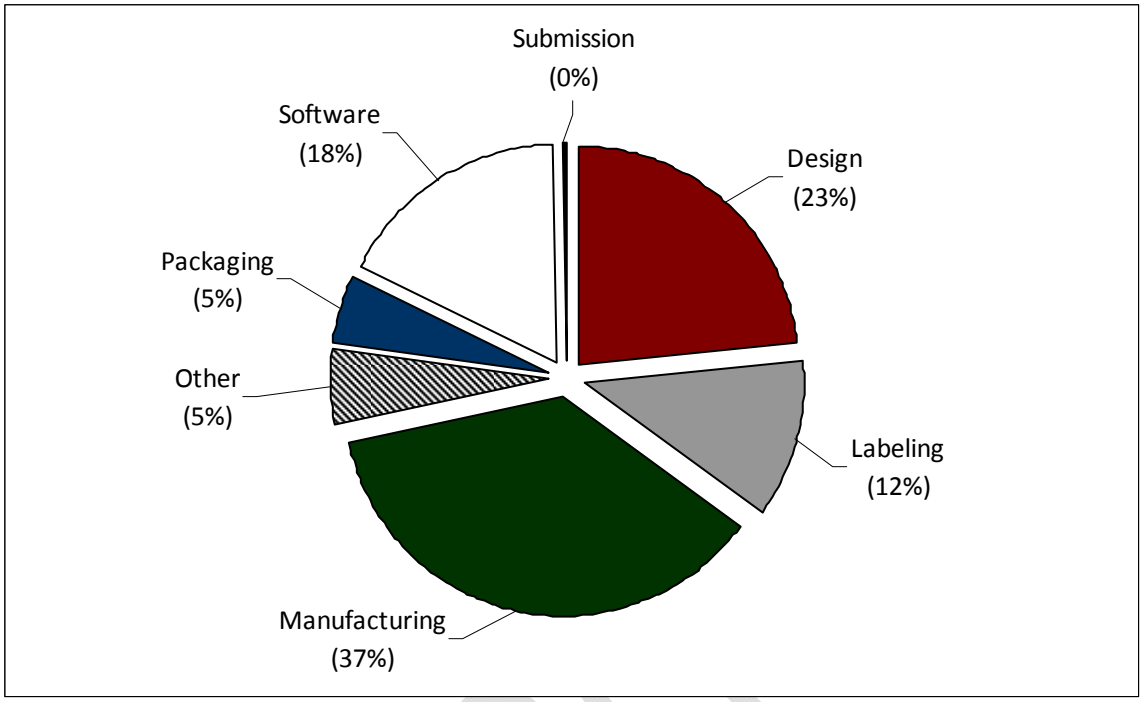
- The 510(k) Working Group further recommends that CDRH continue its ongoing effort to implement a unique device identification (UDI) system and consider, as part of this effort, the possibility of using "real-world" data (*e.g.*, anonymized data on device use and outcomes pooled from electronic health record systems) as part of a premarket submission for future 510(k)s.

Manufacturing Process Information. In some circumstances, it may be necessary for a submitter to provide manufacturing process and design control information as part of its 510(k). For example, in cases where an SE decision depends on device performance remaining within a narrow range, as in the case of some diagnostic tests used to guide treatment decisions,[168] and where there may be variability in performance between manufactured lots, it may be necessary for CDRH to assess the means by which a firm tests its lots. In addition, manufacturing processes and quality testing procedures may have a significant bearing on device safety and/or effectiveness, particularly for devices that use novel materials and 510(k)s submitted to address a recall or as a "corrective fix" to an identified problem. There may be, in some circumstances, a substantial likelihood that failure to comply with good manufacturing requirements will potentially present a serious risk to human health. Due to insufficient guidance and training, Center review staff are not fully informed of their ability to request manufacturing process information as part of their review, or the situations in which such information is necessary to support clearance.

Issues related to manufacturing can have a significant public health impact. As shown in Figure 5.5, below, 37 percent of device recalls from 2005 through 2009 were associated with manufacturing problems. Without clear guidelines on when it may be appropriate to request manufacturing process information, it can be difficult for reviewers and submitters to know when such information is to be expected as part of a 510(k).

[168] For example, to satisfy minimum performance standards, glucose meters must provide blood glucose readings within 20 percent of the true blood glucose value.

Figure 5.5. Recalls of 510(k) Devices by Cause [169]



Beyond requesting manufacturing process information, there may be circumstances in which a pre-clearance facility inspection may be necessary to demonstrate that a device, when marketed, will not present a health risk. Section 513(f)(5) of the FDCA[170] states, "[FDA] may not withhold a determination of the initial classification of a device… because of a failure to comply with any provision of this Act unrelated to a substantial equivalence decision, including a finding that the facility in which the device is manufactured is not in compliance with good manufacturing requirements as set forth in regulations of [FDA] under section 520(f) (*other than a finding that there is a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health*)" (emphasis added). To date, FDA has been reluctant to apply its authority to require pre-clearance inspections. When it does so, it is usually on a case-by-case basis in situations where individual submitters have a history of non-compliance that creates an elevated level of concern.

- The 510(k) Working Group recommends that CDRH develop guidance to provide greater clarity regarding what situations may warrant the submission of manufacturing process information as part of a 510(k), and include a discussion of such information as part of its "class IIb" guidance.

- The 510(k) Working Group further recommends that CDRH clarify when it is appropriate to use its authority to withhold clearance on the basis of a failure to comply with good manufacturing requirements in situations where there is a substantial likelihood that such failure will potentially present a serious risk to human health, and include a discussion of pre-clearance inspections as part of its "class IIb" guidance.

[169] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Submission" refers to devices that were recalled after it was determined that the manufacturer had not provided an appropriate premarket submission for the device.

[170] 21 USC §360c(f)(5).

5.2.1.4. Incorporation of New Information into 510(k) Decision Making

CDRH uses science to guide its regulatory decision making across the total product life cycle of medical devices. At any stage of that life cycle, the Center may encounter new, unfamiliar, or unexpected scientific information that may influence its thinking, expectations, and actions. Sometimes, for example, new safety information comes to light about a given device or device type on the market that might lead the Center to modify its premarket evidentiary expectations for future devices of the same type in order to prevent similar problems from recurring. While there is broad agreement across and outside of the Center that it is important for public health that review decisions consider all relevant safety and effectiveness information, it has been challenging to incorporate new scientific information into premarket decision making while also providing as much predictability as practical. This issue is discussed more fully in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.

5.2.2. Finding: Limitations in CDRH's information technology (IT) and knowledge management infrastructure and tools make it challenging for Center staff and 510(k) submitters to access meaningful medical device information that would support better-informed and more predictable decision making.

Recommendation: CDRH should take steps to enhance its internal and public information systems and databases to provide easier access to more complete information about 510(k) devices and previous clearance decisions.

To optimally make use of the information it receives about 510(k) devices, CDRH needs an IT-supported knowledge management system that allows for efficient knowledge-development and knowledge-sharing. Because 510(k) decision making relies on a comparison to a predicate, both review staff and submitters must have an adequate level of familiarity with predicate devices and past 510(k) decisions, supported by well-organized and readily accessible information, in order for the process to function properly.

5.2.2.1. Product Codes

CDRH identifies medical device types using three-character "product codes." The product code system was originally developed as a tool for device listing by registered device establishments.[171] As described in Section 4.1, above, CDRH initially classified preamendment device types through rulemaking after the passage of the MDA, in order to establish the agency's device classification regulations. At that time, each classification regulation was assigned at least one product code. Over time, as new devices with different indications for use or different technological characteristics were found substantially equivalent to predicate devices within a given classification regulation, new product codes were created and added to each regulation. Product codes were intended to bridge the gap between the general descriptive language provided in the classification regulations and the more granular distinctions between specific devices within each regulation.

[171] Procedures for domestic device establishments regarding registration and listing are provided in 21 CFR 807 Subpart B.

Example: Product Code Evolution

Stereotaxic instruments are regulated under the classification regulation 21 CFR 882.4560. They are identified as devices "consisting of a rigid frame with a calibrated guide mechanism for precisely positioning probes or other devices within a patient's brain, spinal cord, or other part of the nervous system."

Through sequential 510(k) substantial equivalence determinations, this device type has evolved to include motorization, computer guidance, and, most recently, robotic surgical systems. In addition, the clinical application of these devices, which originally only included neurologic indications, has evolved over time to include orthopedic surgery (with numerous specific surgical procedures) and open liver surgical procedures. To track these innovations, the following product codes have been established within the classification regulation:

- HAW – Neurological Stereotaxic Instrument (This is the product code for the original preamendment device type upon which the classification regulation was based.)
- ONN – Intraoperative Orthopedic Joint Assessment Aid
- OJP – Orthopedic Computer Controlled Surgical System
- OLO – Orthopedic Stereotaxic Instrument
- OEW – Intraoperative Soft Tissue Tracking

Thus, over time, a classification regulation that describes a mechanical frame for neurological indications has grown to accommodate several different device types with various clinical indications and levels of complexity.

Over the past three decades, product codes have become the underpinning for CDRH's information management systems. Product codes are the primary tool for organizing medical device information in CDRH's databases, and staff across the Center rely on product codes in their day-to-day work. Product codes are used for tracking and analysis of medical device data across a device's total product life cycle, including information from premarket submissions, adverse event reports, device recalls, inspections, and compliance actions. Review staff and 510(k) submitters use product code searches to identify and obtain additional information about potential predicate devices.

When a device is cleared, CDRH identifies the device's product code in its SE letter to the submitter.[172] In some cases, a new device is assigned a product code that already exists. In other cases, as described above, a new product code is created to differentiate the new product's features or functions. Although CDRH has procedures in place for creating new product codes, it has not established uniform criteria for assigning new or existing product codes.

Inconsistencies in the way product codes are developed and assigned make it challenging to readily access meaningful device information through a product code search. Some product codes, for example, cover a broad range of devices, which can make it difficult to access specific device information. Other product codes are very narrow, which can make it challenging to identify cross-cutting issues among similar or related devices. In addition, there is no systematic method for assigning product codes for multiplex devices, which are comprised of assays for multiple analytes. Some multiplex devices are assigned their own product codes, others are assigned the product code of one of their component assays, and still others are assigned several product codes, each of which is associated

[172] The manufacturer must then list its new device using the product code provided.

with one of their component assays. Without a consistent organizational approach, it can be difficult for Center staff to know how to find relevant device information.

To date, the focus of CDRH's product code management has been limited to maintaining the product code database and coordinating the creation, modification, and organization of the codes. The Center has not yet taken a comprehensive approach to product code management that fully considers how product codes should be developed and assigned to optimally support the Center's programmatic functions. Further, as illustrated in the example below, it may be difficult to determine the optimal level of granularity for product codes.

Example: Assignment of Product Codes

Surgical lasers are regulated under the classification regulation 21 CFR 878.4810. They are identified as devices "intended to cut, destroy, or remove tissue by light energy" emitted continuously.

Lasers are technologically different from light-based medical devices such as an Intense Pulse Light (IPS). However, light-based medical devices were determined to be substantially equivalent to surgical lasers under the same classification regulation and product code, GEX.

The agency later determined that the use of the same product code for different technologies was problematic because laser-specific performance standards did not apply uniformly across devices classified under the GEX product code. As a result, a new product code was retrospectively created for light-based devices. This action required the issuance of corrected SE letters for all light-based devices.

It was also determined that product codes should differentiate between over-the-counter and prescription devices within the surgical laser classification regulation. Currently, there are twelve product codes under this classification regulation. It is possible that additional product codes could be created in the future to further differentiate this device type by indication for use, wavelength, pulsed/continuous emission, etc.

- The 510(k) Working Group recommends that CDRH develop guidance and Standard Operating Procedures (SOPs) on the development and assignment of product codes, in order to standardize these processes and to better address the information management needs of the Center's staff and external constituencies.

- The 510(k) Working Group further recommends that CDRH enhance existing staff training on the development and assignment of product codes.

5.2.2.2. 510(k) Databases

CDRH's review staff and external constituencies rely on the Center's databases to obtain information about cleared devices and previous 510(k) decisions. Ready access to such information supports both goals of the 510(k) program: it helps reviewers and managers make better-informed decisions, and it increases predictability by providing prospective 510(k) submitters with insight into the Center's expectations. Both staff and the Center's external constituencies have identified areas for improvement with respect to CDRH's databases.

Limited Tools for Review Staff. CDRH review staff do not currently have reliable, ready access to meaningful information about past 510(k) decisions: there is no easily searchable internal database of detailed information on previous clearances.

The only comprehensive electronic source of non-public information on prior reviews available to Center staff is a database of archived image files of cleared 510(k)s. The database is searchable only by 510(k) number. To find information within each file, staff must conduct a labor-intensive, file-by-file text search. Without looking through each file individually, it is impossible to determine what predicate(s) the reviewer used as the basis for a substantial equivalence determination, and what the rationale for the decision was. Moreover, archived files contain varied levels of detail. Older 510(k) submissions and review memoranda tend to be inconsistent in format and content, and many of them are handwritten. The 510(k) decision making criteria and flowchart were not introduced until 1986, and the first standardized format for review memoranda was not developed until 1990. As mentioned in Section 5.1.1.1, above, the publicly released "Indications for Use" form was not adopted until 1996. Documentation of the rationale for older review decisions may therefore be limited. Even now, inadequate staff training and the absence of an automated knowledge management system may result in insufficiently documented decisions. Due to the limitations of CDRH's internal database, review staff must conduct time-consuming searches or rely on institutional knowledge and individual experience when trying to identify an appropriate predicate or seeking information on past decisions that might be relevant to a 510(k) under review.

Insufficient information about what was cleared in previous 510(k)s and the rationale for earlier decisions makes it more challenging for CDRH reviewers and managers to make fully informed substantial equivalence determinations. It can be difficult and time-consuming to identify what intended use, technological characteristics, and performance data were reviewed and cleared for a predicate device, which can make it challenging for review staff to conduct a complete comparison between all relevant aspects of the predicate and the new device. Special 510(k)s for device modifications present an even greater challenge because they generally contain little to no performance data and are not readily linked to the pre-modification predicate 510(k)s on which they were based. It can be difficult to trace the review history when a new device cites a Special 510(k) as a predicate, or when several Special 510(k)s for the same device are submitted in succession, each citing the previous one.

Limited Tools for Outside Parties. The primary public source of information on CDRH's 510(k) review decisions is the Center's online 510(k) database.[173] After a device has been cleared, ODE and OIVD post on the database the SE letter and "Indications for Use" form for the device, as well as the submitter's 510(k) summary or statement.[174] In addition, OIVD posts a "decision summary," written by review staff, that includes a summary of submitted data and a comparison of the new device to the predicate. The database is searchable by a variety of fields, including classification panel, product code, 510(k) number, applicant name, device name, and decision date.

Public comments generally indicated that the 510(k) database is useful, but many recommended adding additional search features, including the ability to search by intended use, materials, predicate device, and any updates to device name or 510(k) holder. Comments also suggested organizing the database so that all related 510(k)s (*e.g.*, a device and its various modifications) are clearly grouped together, and so

[173] The 510(k) database is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

[174] As specified by 21 CFR 807.87(h), a 510(k) must contain a "510(k) summary as described in 807.92 or a 510(k) statement as described in 807.93."

that bundled devices are more clearly identified as such.[175] In addition, both staff and public comments noted that submitters' 510(k) summaries are often vague and lack meaningful information on which a prospective submitter could base a future 510(k). Further, staff reported that these summaries may be inconsistent with review memoranda. Some public comments stated that 510(k) statements are not an adequate substitute for 510(k) summaries, because they do not provide information about the device or the review decision. There was a general consensus among public comments that OIVD's decision summaries are very helpful, and many recommended that ODE provide similar summaries.

Beyond CDRH's online 510(k) database, prospective 510(k) submitters and members of the public have the option of requesting full, redacted 510(k)s under the Freedom of Information Act (FOIA). Comments noted, however, that these requests take a long time to fill, and much of the most important or relevant information may be redacted.

Publicly providing accurate and meaningful information about previous 510(k) decisions and predicate devices is essential to increasing the transparency and predictability of CDRH's 510(k) decision making. Without an understanding of the basis for a predicate's clearance, it may be difficult for prospective 510(k) submitters to select an appropriate predicate. Lacking a reliable source of accurate information, 510(k) submitters may look to how the predicate is advertised, which does not necessarily reflect the intended use for which it was cleared. In addition, providing information about the basis for previous 510(k) decisions can provide much-needed clarity about CDRH's evidentiary expectations and decision-making rationale.

- The 510(k) Working Group recommends that CDRH develop a publicly available, easily searchable database that includes, for each cleared device, a verified 510(k) summary, photographs and schematics of the device, to the extent that they do not contain proprietary information, and information showing how cleared 510(k)s relate to each other and identifying the premarket submission that provided the original data or validation for a particular product type.

- The 510(k) Working Group further recommends that CDRH develop guidance and SOPs for the development of 510(k) summaries to assure they are accurate and include all required information identified in 21 CFR 807.92. The Center should consider developing a standardized electronic template for 510(k) summaries.

Lack of Ready Access to Final Device Labeling. Despite a statutory provision that explicitly requires device manufacturers to submit the label and package insert for a device and a representative sampling of any other labeling for the device, FDA does not routinely obtain and review such labeling for devices other than those with approved PMAs. Section 510(j) of the FDCA[176] requires certain manufacturers, at the time of registration and listing, to submit not only a list of their devices, but also certain labeling.[177]

[175] An additional challenge identified by Center staff is that, when a class II (510(k)) device is bundled with a class III (PMA) device, the devices are reviewed together under the PMA process, and no 510(k) summary or statement is provided publicly for the class II components of the application.

[176] 21 USC §360(j).

[177] For devices subject to a performance standard under section 514 or subject to section 515, section 510(j)(1)(A) requires the registrant to submit "a reference to the authority for the marketing of the device and a copy of all device labeling." For restricted devices, section 510(j)(1)(B)(i) requires the submission of "a copy of all labeling[,] … a representative sampling of advertisements and, upon request made by [FDA] for good cause, a copy of all advertisements…." For non-restricted devices, section 510(j)(1)(B)(ii) requires the registrant to submit "the label and package insert for such… device and a representative sampling of any other labeling for such [device]." If a device is not subject to a performance standard under section 514, is not subject to section 515, or is not a restricted device, section 510(j)(1)(D) states that the listing must be accompanied by "a brief

FDA's implementing regulations, however, require only that registrants submit such information "upon specific request."[178]

Because CDRH does not typically obtain and review final product labeling for 510(k) devices, it is difficult for the Center to assure that the labeling of each marketed 510(k) device is consistent with its clearance. Inconsistencies between the basis for a device's clearance and the way that device is labeled can create challenges for prospective 510(k) submitters in selecting an appropriate predicate. Such inconsistencies can also create challenges for medical professionals and device users, who may rely on labeling in order to use a cleared device safely and effectively.

If manufacturers of 510(k) devices electronically submitted their final device labeling to FDA and provided periodic labeling updates to the agency, CDRH could screen this information and include updated, cleared labeling as part of the public 510(k) database described above. This could provide a tremendous service to both industry and the user community. Some manufacturers already provide electronic versions of their current device labeling on their company websites. Featuring up-to-date, cleared device labeling in CDRH's public 510(k) database would allow prospective 510(k) submitters to more readily and more accurately compare their devices to potential predicates, and it would give medical professionals and device users easy access to critical device information that would support safe and effective use.[179]

- The 510(k) Working Group recommends that CDRH revise existing regulations to clarify the statutory listing requirements for submission of labeling. CDRH should also explore the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable period of time after clearance, and also to provide regular, periodic updates to device labeling, potentially as part of annual registration and listing or through another structured electronic collection mechanism. If CDRH adopts this approach, updated labeling should be posted as promptly as feasible on the Center's public 510(k) database after such labeling has been screened by Center staff to check for consistency with the device clearance. In exploring this approach, CDRH should consider options to assure that labeling could be screened efficiently, without placing a significant additional burden on review staff. For example, to allow for more rapid review of labeling changes, the Center could consider the feasibility of requiring manufacturers to submit a clean copy and a redlined copy of final labeling and subsequent updates, highlighting any revisions made since the previous iteration. As a longer-term effort, the Center could explore greater use of software tools to facilitate rapid screening of labeling changes. The Center should consider phasing in this requirement, potentially starting with only a subset of devices, such as the "class IIb" device subset described above, or with a particular section of labeling. CDRH should also consider posting on its public 510(k) database the version of the labeling cleared with each submission as "preliminary labeling," in order to provide this information even before the Center has received and screened final labeling.

Limited Information on Current 510(k) Ownership. CDRH's databases rarely reflect changes in 510(k) ownership that occur after clearance, largely because the Center is not typically notified of transfers of

statement of the basis upon which the registrant made such determination if [FDA] requests such a statement with respect to that particular… device." Section 510(j)(2)(D) requires the submission of "Any material change in any information previously submitted…."

[178] 21 CFR 807.31(e).

[179] An additional benefit of periodically collecting updated device labeling is that it would enable FDA to determine if there has been a change in labeling that would warrant submission of a new 510(k).

ownership. Current law and regulations do not expressly require the initial 510(k) holder notify FDA when a transfer of ownership occurs.

Lack of up-to-date 510(k) ownership information creates a number of challenges for FDA, and for 510(k) holders and submitters. When a transfer of ownership takes place and the new 510(k) holder lists the device with FDA, it can be difficult for the agency to verify the new ownership. When a device is listed by an entity other than the original 510(k) holder without reference to the number assigned to the original 510(k) submission, it can be challenging for FDA to confirm that the device has, in fact, been cleared.[180] In addition, when a new 510(k) cites a predicate device using the name of the new owner, but does not provide the predicate's 510(k) number, it can be challenging and time-consuming to tie the cited predicate to an actual 510(k) clearance. This creates delays for both review staff and the submitter. Moreover, without accurate, up-to-date knowledge of 510(k) ownership, FDA may have difficulty taking device-specific actions in a timely manner, including communicating relevant information to the 510(k) holder or addressing any public health concerns related to the device in question.

A large majority of public comments supported FDA's exercising greater authority to require information about the transfer of 510(k) ownership. Many comments encouraged the agency to issue guidance on the appropriate procedures for reporting transfers of ownership.

- The 510(k) Working Group recommends that CDRH develop guidance and regulations regarding appropriate documentation of transfers of 510(k) ownership. The Center should update its 510(k) database in a timely manner when a transfer of ownership occurs.

5.3. Continuous Quality Assurance

In addition to providing greater clarity to review staff and submitters about the 510(k) review standard and CDRH's expectations for submissions, the Center must have systems and tools in place to continuously assure the quality and consistency of 510(k) reviews. Quality and consistency depend on a highly qualified, well-trained, and well-supported review staff, and on appropriate oversight.

5.3.1. Finding: Variations in the expertise, experience, and training of reviewers and managers, including third-party reviewers, may contribute to inconsistency or uncertainty in 510(k) decision making.

Recommendation: CDRH should enhance training, professional development, and knowledge-sharing among reviewers and managers, in order to support consistent, high-quality 510(k) reviews.

Making sure that the individuals involved in each 510(k) review, including both in-house review staff and third-party reviewers, have appropriate scientific expertise and regulatory experience is essential to both the quality of the review and the consistency of the program.

[180] Some 510(k) holders improperly and illegally treat a 510(k) as a license and assign manufacturing rights to a number of entities under a single 510(k) number.

5.3.1.1. Reviewer Expertise and Experience

Variations in staff expertise and experience can have an impact on 510(k) reviews. Given the heterogeneity of 510(k) devices with respect to both technology and clinical applications, CDRH must maintain a large cadre of experts across many disciplines and subspecialties. At times, the Center may supplement its in-house expertise with the knowledge of outside experts, particularly when dealing with novel technologies. However, CDRH can only effectively leverage external expertise if it has staff with training in the same areas to properly vet and integrate the input provided.

Staff and manager turnover can adversely affect the consistency of 510(k) data requests and regulatory decision making in general. Turnover of staff during a review and insufficient training for new staff may result in delays and inadequately documented review decisions. Newer or less trained review staff may not have the expertise or experience needed to identify all of the critical issues in a given 510(k), particularly when the submitter has not clearly characterized the relevant points of comparison between the new device and the predicate, as discussed in Section 5.2.1.2, above. Further, new reviewers and managers may lack familiarity with the history of a given device, including common problems, or they may ask questions that have already been addressed and resolved in previous submissions.

Comments from industry consistently cited reviewer experience as a critical factor in the review of a 510(k). Comments asserted that less experienced reviewers tend to request additional information, including clinical data, as discussed in Section 5.2.1.3. The 510(k) Working Group analyzed data on reviewer experience and various 510(k) outcomes.[181] These data suggest a correlation between reviewer experience and more efficient reviews; however, the trends do not appear strong. Figure 5.6, below, shows the percentage breakdown of 510(k)s in the Working Group's data set reviewed by individuals with various years of experience. As shown in Tables 5.8, 5.9, and 5.10, below, less experienced reviewers may be more likely to have lengthier review memoranda, more review cycles, and more withdrawals than more experienced reviewers.

[181] "Reviewer experience" refers to the length of time between a reviewer's first 510(k) and a given 510(k) within the Working Group's data set.

Figure 5.6. Years Reviewer Experience [182]

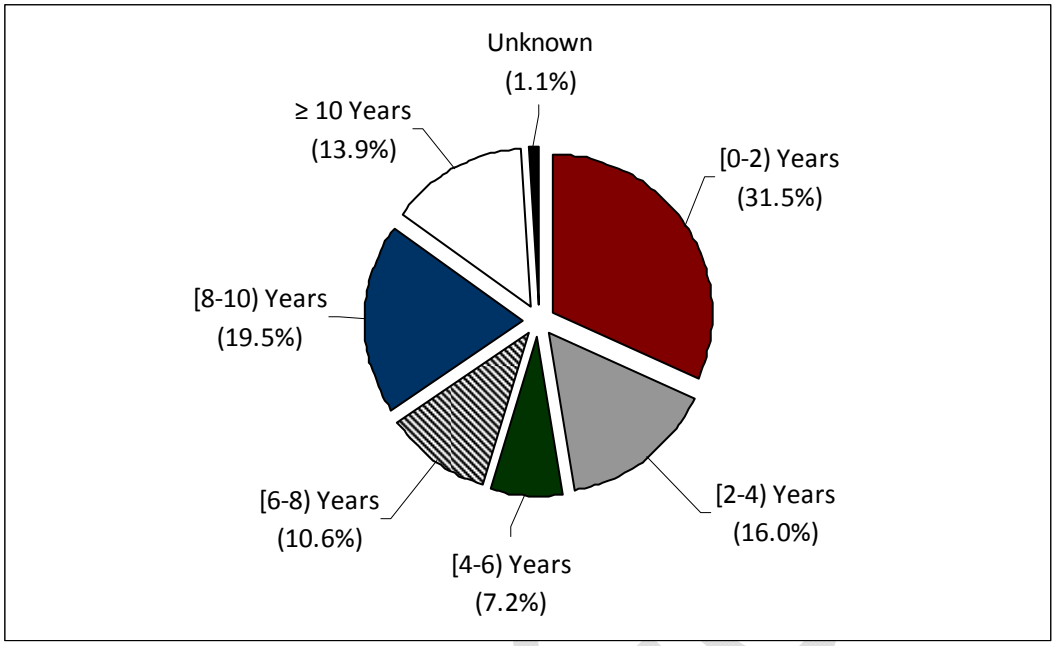


Table 5.8. Review Memo Page Count by Years Reviewer Experience [183]

Years Experience	Mean Page Count	< 20 Pages % (#)	20-59 Pages % (#)	60-99 Pages % (#)	≥ 100 Pages % (#)	# Pages Unknown % (#)	All % (#)
[0-2)	40.9	22.1% (1,278)	31.3% (1,808)	7.3% (425)	4.8% (277)	34.5% (1,995)	100% (5,783)
[2-4)	41.7	24.5% (720)	31.6% (929)	7.3% (214)	5.5% (162)	31.2% (917)	100% (2,942)
[4-6)	33.4	27.3% (361)	26.7% (354)	5.1% (68)	2.5% (33)	38.4% (508)	100% (1,324)
[6-8)	33.3	33.8% (660)	23.9% (466)	4.6% (89)	3.1% (60)	34.6% (675)	100% (1,950)
[8-10)	30.5	45.4% (1,627)	36.9% (1,322)	5.8% (208)	3.2% (114)	8.7% (310)	100% (3,581)
≥ 10	37.0	19.5% (497)	17.3% (440)	3.3% (84)	2.8% (72)	57.1% (1,453)	100% (2,546)

[182] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Reviewer experience" refers to the length of time between a reviewer's first 510(k) and a given 510(k) within the Working Group's data set. "Unknown" indicates missing data. Values may not sum to 100 percent due to rounding.

[183] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Reviewer experience" refers to the length of time between a reviewer's first 510(k) and a given 510(k) within the Working Group's data set. "Unknown" indicates missing data. Values may not sum to 100 percent due to rounding.

Years Experience	Mean Page Count	< 20 Pages % (#)	20-59 Pages % (#)	60-99 Pages % (#)	≥ 100 Pages % (#)	# Pages Unknown % (#)	All % (#)
Unknown	7.7	31.1% (64)	1.9% (4)	—	—	67.0% (138)	100% (206)
All	36.5	28.4% (5,207)	29.0% (5,323)	5.9% (1,088)	3.9% (718)	32.7% (5,996)	100% (18,332)

Table 5.9. Number of Review Cycles by Years Reviewer Experience [184]

Years Experience	Mean # Review Cycles	1 Cycle % (#)	2 Cycles % (#)	3 Cycles % (#)	4 Cycles % (#)	≥ 5 Cycles % (#)	All % (#)
[0-2)	1.84	41.0% (2,371)	37.2% (2,149)	18.9% (1,095)	2.5% (144)	0.4% (24)	100% (5,783)
[2-4)	1.81	42.9% (1,263)	35.9% (1,057)	18.6% (547)	2.4% (71)	0.1% (4)	100% (2,942)
[4-6)	1.80	42.4% (561)	38.0% (503)	17.5% (232)	1.9% (25)	0.2% (3)	100% (3,581)
[6-8)	1.70	50.0% (975)	32.4% (631)	15.6% (304)	1.7% (34)	0.3% (6)	100% (1,950)
[8-10)	1.63	54.1% (1,937)	30.7% (1,098)	13.9% (498)	1.3% (45)	0.1% (3)	100% (3,581)
≥ 10	1.71	48.4% (1,232)	35.5% (905)	13.7% (349)	2.0% (50)	0.4% (10)	100% (2,546)
Unknown	1.56	72.8% (150)	9.7% (20)	9.7% (20)	4.9% (10)	2.9% (6)	100% (206)
All	1.75	46.3% (8,489)	34.7% (6,368)	16.6% (3,045)	2.1% (379)	0.3% (56)	100% (18,332)

[184] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Reviewer experience" refers to the length of time between a reviewer's first 510(k) and a given 510(k) within the Working Group's data set. "Unknown" indicates missing data. Values may not sum to 100 percent due to rounding.

Table 5.10. 510(k) Decision Type by Years Reviewer Experience [185]

Years Experience	SE % (#)	NSE % (#)	Withdrawn % (#)	Deleted % (#)	Other % (#)	All % (#)
[0-2)	84.1% (4,863)	3.6% (210)	4.1% (235)	7.1% (411)	1.1% (64)	100% (5,783)
[2-4)	85.2% (2,506)	2.8% (81)	4.7% (138)	6.2% (183)	1.2% (34)	100% (2,942)
[4-6)	84.7% (1,121)	2.6% (34)	4.5% (59)	6.7% (89)	1.6% (21)	100% (3,581)
[6-8)	84.3% (1,643)	3.6% (70)	3.2% (62)	7.3% (142)	1.7% (33)	100% (1,950)
[8-10)	86.1% (3,085)	3.4% (70)	3.2% (116)	5.8% (209)	1.4% (49)	100% (3,581)
≥ 10	84.2% (2,144)	3.2% (81)	3.3% (84)	6.5% (166)	2.8% (49)	100% (2,546)
Unknown	17.5% (36)	2.9% (6)	10.7% (22)	58.7% (121)	10.2% (21)	100% (206)
All	84.0% (15,398)	3.3% (604)	3.9% (716)	7.2% (1,321)	1.6% (293)	100% (18,332)

In addition to the experience level of individual reviewers, another factor that is critical to quality and consistency is the ability of staff across CDRH to work seamlessly with one another on cross-cutting issues. Because some devices are a combination of two or more devices (such as a glucose meter that is combined with an infusion pump), more than one division or office may be involved in the review process. It is particularly critical in these cases to have a common understanding of data needs and decision making criteria. Currently, the Center does not have a cross-cutting mechanism for sharing knowledge about premarket review decisions and approaches.

As part of the Center's FY 2010 Strategic Priorities, CDRH is working to improve recruitment, retention, and staff professional development, including drawing on the knowledge of external experts. In addition, the Center is in the process of implementing an interactive software system called iReview, which will be used to support 510(k) reviews in both ODE and OIVD by the end of 2010. iReview is designed to lead reviewers through a standardized review process, featuring built-in templates, checklists, and training tools. CDRH is also exploring the possibility of undertaking organizational changes to more effectively support Center-wide integration.

[185] Data shown are from CDRH's databases. *See* Section 3.4.2 for a discussion of the Working Group's data collection and analysis. "Reviewer experience" refers to the length of time between a reviewer's first 510(k) and a given 510(k) within the Working Group's data set. SE includes SE, SE with Limitations, CLIA – SE, and SE – Kit. "CLIA SE" refers to devices that receive a Clinical Laboratory Improvement Act (CLIA) categorization along with the SE decision. "SE – Kit" refers to devices that are cleared as a kit, *i.e.*, preamendment, exempt, or cleared devices packaged together without a new intended use. "Unknown" indicates missing data. Values may not sum to 100 percent due to rounding.

- The 510(k) Working Group recommends that CDRH continue to take steps to enhance recruitment, retention, training, and professional development of review staff, including providing opportunities for staff to stay abreast of recent scientific developments and new technologies. This should include increased engagement with outside experts, as discussed further in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.

- The 510(k) Working Group further recommends that CDRH consider establishing a Center Science Council comprised of experienced reviewers and managers and under the direction of the Deputy Center Director for Science. Consistent with the President's memorandum on scientific integrity,[186] the Science Council should serve as a cross-cutting oversight body that can facilitate knowledge-sharing across review branches, divisions, and offices, consistent with CDRH's other ongoing efforts to improve internal communication and integration. The Science Council's role in improving the consistency of Center decisions more broadly is discussed in greater detail in the preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making.

5.3.1.2. Third-Party Review

As described in Section 4.3.2.2, above, the 510(k) third-party review program was established under FDAMA. According to Section 523(a)(3) of the FDCA,[187] certain devices are ineligible for third-party review: class III devices; class II devices that are intended to be permanently implantable, life-sustaining, or life-supporting; and, in general, class II devices for which clinical data is required.[188] When FDA initially implemented the program, only device types with device-specific guidance were considered eligible for third-party review. In 2001, however, the program was expanded to include all class II devices not specifically excluded by statute, including those for which no device-specific guidance exists.

Over the past five years, third-party submissions have accounted for approximately seven percent of all 510(k)s received by CDRH, as shown in Figure 5.7, below. Third-party reviews appear to have resulted in more rapid clearance decisions for these devices: during FY 2008, 510(k)s reviewed by third parties were cleared in an average of 104 days after initial receipt by the third party — 17 percent faster than third-party–eligible 510(k)s reviewed entirely by CDRH (126 days). Despite this apparent benefit, concerns have been raised about the quality of third-party submissions.

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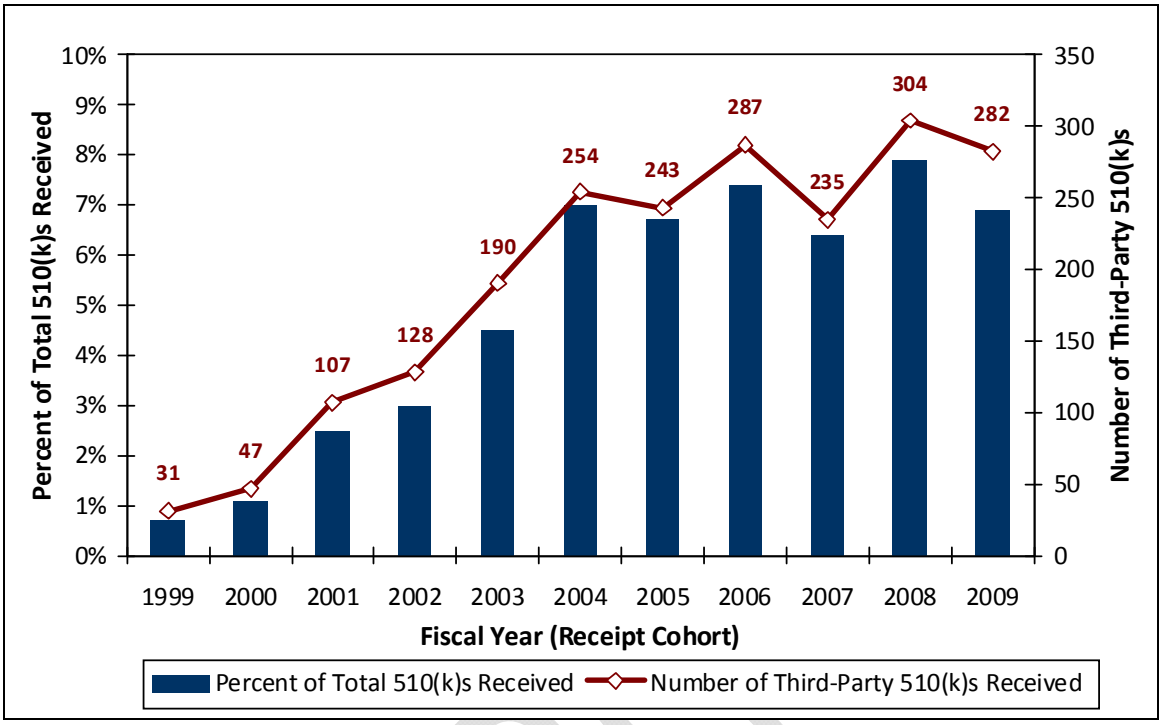
[186] Obama B, Memorandum for the Heads of Executive Departments and Agencies (March 9, 2009). Available at: http://www.whitehouse.gov/the_press_office/memorandum-for-the-heads-of-executive-departments-and-agencies-3-9-09/.

[187] 21 USC §360m(a)(3).

[188] Specifically, section 523(a)(3)(A) of the FDCA (21 USC §360m(a)(3)(A)) states, "In general. An accredited person may not be used to perform a review of — (i) a class III device; (ii) a class II device which is intended to be permanently implantable or life sustaining or life supporting; or (iii) a class II device which requires clinical data in the report submitted under section 510(k) for the device, except that the number of class II devices to which [FDA] applies this clause for a year, less the number of such reports to which clauses (i) and (ii) apply, may not exceed 6 percent of the number that is equal to the total number of reports submitted to the Secretary under such section for such year less the number of such reports to which such clauses apply for such year."

Figure 5.7. Third-Party 510(k)s as a Percentage of Total 510(k)s Received: FY 1999-2009



In a May 2007 report to the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions,[189] FDA provided information on quality issues that had been observed with third-party reviews during the last nine months of FY 2005. This information is shown in Table 5.11, below. The report concluded that the third-party review program is useful, but it also highlighted quality concerns and pointed out the need for more device-specific guidance for third-party-eligible device types.

Table 5.11. Frequency of Issues with Third-Party Reviews of 510(k)s [190]

Review Element	% Rated as Minor Issue	% Rated as Major Issue	% Major or Minor
Pre-submissions consultation with FDA	15%	4%	19%
Rationale for conclusions and recommendations	11%	6%	17%
Comparison to legally marketed devices — identification and analysis of key similar. & diff.	11%	5%	16%
Summary of device characteristics, intended use,	10%	4%	14%

[189] von Eschenbach AC, "Third Party Review of Medical Device Premarket Notifications," Report to the Committee on Energy and Commerce, U.S. House of Representatives, and the Committee on Health, Education, Labor, and Pensions, U.S. Senate (May 2007).

[190] *Id.* at 21. These data are based on quality assessments completed by FDA supervisors when making a final determination on 510(k)s with a third-party review. FDA initiated the quality assessments in January 2005. Quality assessments were completed for 75 percent of third-party reviews received during the last 9 months of FY 2005. Overall, minor or major issues were observed with 46 percent of the assessed reviews. Supervisors rated an issue as minor or major based on the extent to which it impacted the acceptability or outcome of a review.

Review Element	% Rated as Minor Issue	% Rated as Major Issue	% Major or Minor
performance, and reason for 510(k)			
Organization and format of review documentation	13%	1%	14%
Use of guidance and standards	10%	2%	12%
Scope of reviewer expertise	8%	3%	11%
Resolution of 510(k) deficiencies and FDA requests	3%	5%	8%
Determination of device eligibility for third-party review	3%	4%	7%
Determination of 510(k) administrative completeness	6%	1%	7%

According to CDRH staff, third parties do not always adequately identify or address 510(k) deficiencies that CDRH considers to be substantive. 49 percent of the third-party submissions received by CDRH in FY 2009 underwent more than one review cycle due to a need for additional information. Although it was intended that Center managers would need to conduct only a high-level assessment of 510(k)s reviewed by a third party, frequently it has been necessary for managers to assign these 510(k)s to in-house reviewers and conduct a comprehensive re-review. Given the 30-day third-party review timeframe,[191] it can be challenging for Center staff to complete an adequate re-review.

Example: Concerns about Third-Party Review Quality

An accredited third party received a 510(k) for a picture archiving and communication system (PACS) device containing nine new software modules and with multiple indications for use. Each software module offered multiple specialized analysis functions specifically intended for a different organ (*e.g.*, brain, lung, etc.). The 510(k) cited twelve unique devices across eight manufacturers as predicates. If such a 510(k) had come directly to FDA for review, it likely would have been treated as a bundled submission, and a separate review would have been conducted for each module.

When FDA received the third-party review, it included only the name and 510(k) number of each predicate cited in the 510(k). It provided no analysis of the similarities and differences between the new device and its twelve predicates in terms of intended use, technological characteristics, or performance.

The third party was notified that a more detailed predicate comparison would be necessary to support a substantial equivalence determination.

A key challenge in the third-party review program is that accredited third parties, unlike in-house reviewers, do not have access to previous 510(k)s, including the 510(k) for a device cited as a predicate, nor do they necessarily have access to new postmarket safety information. As described in Section 5.2.2.2, above, publicly available information about the predicate device cited in a new 510(k) may not provide sufficient information to determine the basis for the predicate's clearance. Without full access to the predicate 510(k), it can be difficult or even impossible for third parties to identify and assess all relevant points of comparison between the new device and the predicate.

[191] Section 523(a)(2)(B) of the FDCA (21 USC §360m(a)(2)(B)).

It is particularly challenging for third-party reviewers to maintain an up-to-date understanding of CDRH's evolving evidentiary expectations in the absence of device-specific guidance. The 2007 report to Congress showed that, among third-party 510(k)s received in FY 2005, those for devices with guidance were more likely to be cleared within a single review cycle.[192]

Concerns have also been raised about the level of training and experience of accredited third parties. CDRH offers training for third-party reviewers, but it is only offered every 3-4 years. Moreover, it covers only general 510(k) program information, not device-specific information.

- The 510(k) Working Group recommends that CDRH develop a process for regularly evaluating the list of device types eligible for third-party review and adding or removing device types as appropriate based on available information. The Center should consider, for example, limiting eligibility to those device types for which device-specific guidance exists, or making ineligible selected device types with a history of design-related problems.

- The 510(k) Working Group further recommends that CDRH enhance its third-party reviewer training program and consider options for sharing more information about previous decisions with third-party reviewers, in order to assure greater consistency between in-house and third-party reviews.

5.3.2. Finding: CDRH does not currently have an adequate mechanism to regularly assess the quality, consistency, and effectiveness of the 510(k) program.

Recommendation: CDRH should enhance its systems and program metrics to support continuous quality assurance.

CDRH's primary tool for assessing the quality of 510(k) reviews is its 510(k) Quality Review Program.[193] Through this program, managers in ODE and OIVD assess a sample of review memoranda on a quarterly basis. A standardized checklist is used to evaluate the completeness of each review memorandum, but not the adequacy or appropriateness of the reviewer's decision making rationale and explanation.

In addition, the Quality Review Program was not designed to provide comprehensive, real-time information about 510(k) program performance. Currently there are insufficient tools and metrics in place to assess the consistency of decision making across the program, and to track the program's public health impact quantitatively. iReview, the interactive software system described above, will store review information as structured data, which will improve CDRH's ability to search and analyze completed reviews. It is expected that this system will better enable CDRH to continuously monitor the 510(k) program; however, it alone will not be an adequate source of program performance data. Further, although CDRH collects information on device performance in the postmarket setting, important limitations, including the inability to consistently link postmarket events to specific 510(k)s, make this information, in isolation, an unreliable measure of program effectiveness. It is possible that CDRH could pool information from multiple internal data sources to develop a sufficiently robust performance profile of 510(k) devices to allow for more meaningful program evaluation.

- The 510(k) Working Group recommends that CDRH develop metrics to continuously assess the quality, consistency, and effectiveness of the 510(k) program, and also to measure the effect of any

[192] *Id.* at 20.

[193] *See* "510(k) Quality Review Program (Blue Book Memo I96-1)" (June 1, 1996). Available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080269.htm.

actions taken to improve the program. As part of this effort, the Center should consider how to make optimal use of existing internal data sources to help evaluate 510(k) program performance.

- The 510(k) Working Group further recommends that CDRH periodically audit 510(k) review decisions to assess adequacy, accuracy, and consistency. The ongoing implementation of iReview, as part of the Center's FY 2010 Strategic Priorities, could assist with this effort by allowing CDRH to more efficiently search and analyze completed reviews. These audits should be overseen by the new Center Science Council, described above, which would also oversee the communication of lessons learned to review staff, as well as potential follow-up action.

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6. CONCLUSION

To support FDA's mission to protect and promote the public health, the Center for Devices and Radiological Health must have in place a quality premarket review process that allows for well-informed, risk/benefit-based decision making and provides a predictable path to market for safe and effective medical devices. Each of the 510(k) Working Group's recommendations represents an area of significant opportunity for CDRH to improve the clarity, quality, and consistency of the 510(k) process.

As the 510(k) Working Group works with other Center staff, after the receipt and review of public comments, to develop an implementation plan for its recommendations, it will also determine an appropriate mechanism and timeframes to evaluate the impact of these actions, and make adjustments as necessary.

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APPENDIX A: SUMMARY OF STAFF FEEDBACK

Throughout the course of its work, the 510(k) Working Group solicited input from other CDRH staff through an Internet-based social media platform called Traction, which is open to all staff. The Working Group also invited staff to provide comments via email and at a Center-wide internal town hall meeting held on February 24, 2010.

This Appendix presents a summary of the comments the Working Group received through these mechanisms.

General Staff Comments

Comments received from CDRH staff were primarily concerned with conducting effective and efficient 510(k) reviews.

Predicates. Comments highlighted the use of questionable predicates, including predicates that had been recalled due to safety issues. Comments also recommended reevaluating CDRH's acceptance of the use of more than one predicate as the basis for a substantial equivalence determination. Comments noted that the use of multiple predicates can be problematic, and that evaluating a submitter's device against all of the predicates cited in a 510(k) and documenting the pathway through the 510(k) flowchart takes a significant amount of time. Comments suggested that, to mitigate confusion, each submitter should explain how a comparison of its device to the chosen predicate(s) would progress through the entire 510(k) flowchart, instead of simply listing proposed predicates in its 510(k) with no explanation. Comments also asserted that the level of scrutiny applied to previous substantial equivalence determinations was inadequate, and that comparisons between submitters' devices and claimed predicates are often inappropriate.

Technological Characteristics. Comments noted that it is challenging to review novel technologies within the 510(k) review timeframe. Some comments recommended revisiting the 510(k) flowchart, suggesting that the questions asked in the 510(k) flowchart may permit unprecedented technology to come to market via the 510(k) program.

Clinical Utility. Comments raised the issue of a device being claimed as a "tool." Comments objected to the expansive application of the term "tool" for devices that are clearly designed for a specific purpose. Although comments indicated that it was appropriate to deem a device that performs a general function a "tool," they stated that the term should not be used for devices designed for a specific purpose. Comments stated that by designating a device designed for a specific purpose as a "tool," health care professionals could reasonably assume that the device had been validated to have at least some clinical utility, when in fact it had not. Comments recommended that, at a minimum, a specialty device being designated as a tool should have a statement in labeling indicating that the clinical utility of the device has not been established.

Level of Evidence. Comments suggested that all clinical studies conducted during development of a 510(k) should be reported in the 510(k), and not merely the clinical studies that were successful or conducted in the United States. Comments also recommended establishing different levels of scrutiny for different device types, based on risk, in order to better adjust to limited review timeframes for 510(k) applications. Comments raised the issue of manufacturing materials and suggested that

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submitters should not only know where their device components originate, but should also be notified by a supplier or manufacturer when a materials or manufacturing change occurs, after which the submitter should notify FDA.

510(k) Database. Comments highlighted deficiencies in the 510(k) database, stating that database contained equivocal historical data on devices and determinations. Moreover, comments stated there was no impetus for reviewers to improve the 510(k) database, and that this potentially valuable tool is deteriorating due to a lack of ownership and contribution.

Communication and Transparency. Comments highlighted the length of time it takes to develop and update guidance, and suggested that CDRH work to streamline the guidance development process. Comments also recommended that CDRH make changes to its website to make it easier for external constituencies to find relevant information.

Resources. Comments emphasized that resources dedicated to reviewing 510(k)s and de novo requests should be allocated more appropriately. Comments stated that the de novo program does not take in to account the resources needed to support that pathway. Comments also suggested that additional resources be dedicated to 510(k)s requiring any clinical input, including minimal clinical data or evaluation of clinical trials.

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APPENDIX B: SUMMARY OF FEBRUARY 18, 2010 PUBLIC MEETING

In its Federal Register notice of January 27, 2010, CDRH announced a public meeting entitled "Strengthening the Center for Devices and Radiological Health's 510(k) Review Process," which was held on February 28, 2010.[194] The purpose of the public meeting was to hear the perspectives of various external constituencies on the 510(k) program, and to identify actions CDRH might consider taking to improve the program.

As described in the notice, the meeting began with presentations by CDRH staff concerning four broad areas of concern identified by the 510(k) Working Group: issues related to predicate devices; issues related to new technologies and scientific evidence; issues related to practices CDRH has adopted in response to a high volume of 510(k) submissions; and issues related to postmarket surveillance and new information about marketed devices. These presentations were followed by a series of prepared presentations and open comments by members of the public on several questions listed in the Federal Register.

The meeting concluded with a roundtable discussion between CDRH staff and selected members of the public, during which participants reflected on the presentations given earlier in the day. The Federal Register notice invited meeting registrants to indicate their interest in participating in the roundtable discussion, and the Working Group selected the discussants with the aim of allowing for a range of different viewpoints to be represented. The discussants were not asked to develop consensus opinions or recommendations, but rather to provide their individual perspectives regarding the 510(k) program.[195]

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[194] "Strengthening the Center for Devices and Radiological Health's 510(k) Review Process; Public Meeting; Request for Comments," 75 Fed. Reg. 17 (Jan. 27, 2010), pp. 4402-4406. Available at http://edocket.access.gpo.gov/2010/2010-1620.htm.

[195] Additional information about the public meeting is available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm193327.htm. The website provides a list of registered speakers and roundtable discussants, as well as links to CDRH staff presentations, a captioned video recording of the meeting, and a verbatim transcript.

APPENDIX C: SUMMARY OF WRITTEN PUBLIC COMMENTS

In its Federal Register notice of January 27, 2010,[196] CDRH solicited comments in response to several questions related to four broad areas of concern identified by the 510(k) Working Group: issues related to predicate devices; issues related to new technologies and scientific evidence; issues related to practices CDRH has adopted in response to a high volume of 510(k) submissions; and issues related to postmarket surveillance and new information about marketed devices. The public docket was open from January 27, 2010 through March 19, 2010.

A total of 81 comments were submitted to the docket. The majority of these comments were submitted by members of the medical device industry (49), while the remainder came from professional associations (18) and unaffiliated individuals (14). The comments primarily included regulatory and policy recommendations, as well as descriptions of respondents' personal experiences with FDA's 510(k) program.

This Appendix presents a summary of these comments. Comments are grouped by topic based on the questions listed in the Federal Register. The number of the question to which each topic corresponds is provided.

General Comments

There were several themes throughout the docket comments that did not specifically answer a question but nevertheless opined on the current state of the 510(k) review process. First and foremost, while the majority of comments indicated the 510(k) process works well, they also recognized that changes are needed. Primarily, many comments emphasized that the success of the 510(k) process is dependent on transparency and predictability on the part of CDRH, and increased communication between CDRH and industry. To this end, numerous comments encouraged CDRH to spend more time developing guidance documents, standards, and other forms of written communication to assist industry in their development of 510(k) submissions. Also, comments encouraged FDA to develop and conduct training programs for reviewers in order to increase consistency.

Many comments expressed concern that increasing the requirements of the 510(k) process would stifle innovation and have a particularly negative impact on small manufacturers, which make up the majority of medical device manufacturers. As a result, device entry to market would be delayed, and patients would be unable to have access to new and improved technologies.

A. Issues Related to Predicate Devices

Q1. Effectiveness of CDRH's 510(k) Database. Comments generally indicated that although the database is a source of useful information, CDRH should make certain improvements. Comments generally stated that the database is useful for searching by product code and 510(k) clearance number. Comments generally suggested updating the database to include the ability to search by: intended use, indications for use, type of testing, materials, predicate devices, and any updates to device names or owners. They also recommended standardizing the format and content of available 510(k) summaries. Some comments recommended improving the product code search function to make it easier to find

[196] "Strengthening the Center for Devices and Radiological Health's 510(k) Review Process; Public Meeting; Request for Comments," 75 Fed. Reg. 17 (Jan. 27, 2010), pp. 4402-4406. Available at http://edocket.access.gpo.gov/2010/2010-1620.htm.

the most appropriate product code for a new product in development. Several comments also emphasized the importance of updating the database more frequently and correcting errors as soon as they are identified. Finally, several comments suggested listing all related 510(k)s in one place, for instance by listing the original and subsequent Special 510(k)s for one device on the same page.

Q2. Sufficiency of Publicly Released 510(k) Documents. There was a general consensus that the staff review decision summaries provided by the Office of In Vitro Diagnostic Device Evaluation and Research (OIVD) are very helpful, and comments recommended that the Office of Device Evaluation (ODE) also make staff decision summaries publicly available. Comments were in general agreement regarding the need for a standard format for decision summaries to assist 510(k) submitters in easily locating desired information. Several comments noted that submitters' 510(k) summaries lack the information on which a future submitter could base a substantial equivalence comparison, and recommended that FDA either update the regulation or issue a guidance defining the content and format for 510(k) summaries. A few comments suggested doing away with the option of a 510(k) statement, and instead requiring a 510(k) summary for all 510(k) submissions.

Q3. Providing Redacted 510(k)s After Clearance. FDA solicited comments on whether or not the agency should require 510(k) holders to submit a redacted version of their 510(k) submission after clearance, for public release. The comments nearly uniformly stated that FDA should not require a redacted version of the 510(k). The primary reason given was that redacted versions of cleared 510(k)s are already available through FDA's Freedom of Information Act (FOIA) office, and, given the amount of information redacted, generally provide very little valuable information. Comments stated that if CDRH implements the recommendations above regarding 510(k) summaries and decision summaries, there would be little need for redacted versions of the 510(k) submissions.

Q4. Inaccurate Portrayal of Similarities and Differences Between Devices. FDA solicited comments on the fact that some 510(k) submitters do not accurately portray the similarities and differences between the device under review and the predicate device(s). Comments generally agreed that the inability for submitters to obtain complete information about predicate devices is a major factor contributing to this issue. A few comments also noted that 510(k) submitters could benefit from access to final product labeling, and thus recommended that CDRH post device labeling in the 510(k) database. One commenter noted that, to the extent FDA states it is routinely receiving 510(k) submissions that fail to adequately provide the information FDA asserts is necessary, FDA should ensure that it has provided industry with clear, concise guidance on the type, amount, and format of the necessary information.

Q5. Use of Older Predicates. FDA requested comments on its generally inclusive strategy of allowing, in general, a device that has been cleared under the 510(k) process to be used as a predicate, regardless of whether or not the device remains relevant to the current standard of care. Although some societies representing health care providers supported the idea of limiting availability for use as a predicate to more recent devices, the majority of comments favored CDRH's current inclusive strategy and stated that CDRH should not limit the devices that may be used as predicates. A primary reason repeated throughout the comments is that FDA has not provided data or information indicating that the use of older or "out-dated" predicates is prevalent or gives rise to the introduction of unsafe or ineffective medical devices. Comments also noted that older devices may have uses for purposes of marketing more cost-effective devices, or for devices for which little change has occurred over a long period of time, *e.g.*, syringes, needles, catheters.

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Q6. Predicate and Non-Inferiority Creep. Comments generally did not express concern about predicate creep, stating that if predicate creep results in a device presenting different questions of safety or effectiveness, or if data do not support the proposition that the device is at least as safe and effective as the predicate device, then CDRH can find the device to be not substantially equivalent. In fact, several comments noted that if "predicate creep" is, in fact, putting onto the market devices that are less safe and effective than competitor products, consumers and health care providers would be unlikely to use such products, and thus market forces may ultimately remove such products from the market.

Further, comments noted that if CDRH has questions about the effect of predicate creep on a substantial equivalence determination, reviewers may request information they deem necessary to support the determination, including a review of modifications for which the submitter did not file a new 510(k).

Q7. Use of "Split Predicates" and "Multiple Predicates." There was nearly universal support for the use of more than one predicate, particularly to avoid using the de novo or premarket approval process for low- to moderate-risk devices for which a single predicate does not exist but that do not necessarily employ new technology. Although comments acknowledged that review of more than one predicate may be more difficult for CDRH, they felt that the benefits generally outweigh the risks. Comments stated that allowing 510(k)s to use more than one predicate is necessary to encourage innovation and keep pace with evolving technology. While comments from industry generally recommended that CDRH continue to allow submitters to cite more than one predicate, comments specifically regarding "split predicates" varied. Most comments stated that CDRH should allow the use of "split predicates," but several of these comments seemed to confuse the concepts of "split predicates" and "multiple predicates": many of the examples cited to support the use of "split predicates" were actually cases in which "*multiple* predicates" were used, such as multi-parameter monitors. However, other comments clearly understood the distinction between these two concepts and supported the use of "split predicates."

Q8. "Indications for Use" Versus "Intended Use." While the majority of the comments described intended use and indications consistent with FDA formal definitions, there were other comments that showed a flawed understanding of the separate terms. Despite the recognized confusion between the terms, a slight majority of the comments recommended that the terms be left separate. Among the reasons cited were the fact that a separation between the terms allows a device to have a different indication for use without it leading to a not substantially equivalent determination, and the fact that such a separation allows submitters to more easily choose a predicate device. There was concern that FDA would not allow for the flexibility of considering new indications for use under the 510(k) program if it combined the terms.

On the other hand, due to the confusion in the terminology and use of the terms interchangeably, numerous comments recommended that the terms be combined.

Guidance was recommended to clarify the issue, regardless of whether the terms were kept separate or combined, in order to better assure consistency.

B. Issues Related to New Technologies and Scientific Evidence

Q1. "Different Technological Characteristics." FDA requested comment on what device features FDA should consider "different technological characteristics," which are defined in section 513(i) of the

FDCA[197] as "a significant change in the materials, design, energy source, or other features of the device from those of the predicate device." The majority of comments stated that FDA should not attempt to define what is meant by "other features," since it would be virtually impossible for FDA to continually revise the list of "other features" to take account of new technology. The comments stated that the language as it exists gives FDA broad latitude to determine what represents "different technological characteristics," and any effort to further define that phrase would only limit FDA's ability to consider new and changing technologies. While the comments did not indicate that defining "other features" is important, they did indicate the importance of determining the significance a change has on the risk analysis of the device.

Q2. De Novo Classification Process. Comments generally indicated that FDA should improve the de novo process and use it more frequently. Suggestions to improve the process included: eliminating the need for FDA to issue a not substantially equivalent determination when both FDA and the manufacturer agree there are no legitimate predicates; establishing a mechanism for early collaboration with the manufacturer and an expedited process for initiating review of de novo requests; issuing additional guidance on the threshold for clearing a device through the de novo process; and adopting a device classification model similar to the Global Harmonization Task Force classification rules.

In determining which risks can be mitigated through general or specific controls, comments suggested the following: determine whether the technology is used or understood in the marketplace; evaluate patient risk and a risk/benefit analysis; consider whether the device is cleared in other countries; evaluate the availability of suitable published industry standards or test methods; and consider whether the results of the clinical or other studies identify an unexpected risk that cannot be adequately controlled through general or special controls. If such a risk has been identified, then use of the de novo process would not be appropriate.

Some comments stated that the de novo process allows clearance of devices for which no reasonable assurance of safety and effectiveness exists. These comments suggested that if FDA finds different questions of safety or effectiveness compared to existing predicates, the device should undergo review through the premarket approval process. Still other comments stated that the need for an efficient de novo process will increase if FDA does not allow use of split predicates, since presumably many of the devices that currently use split predicates do not have one legitimate predicate, but also do not present the risks generally associated with class III devices.

Q3. Characterizing the Risks of New Technology. Comments indicated that FDA should provide more clarity (guidance) on how the agency determines whether a new device raises "different types of safety and effectiveness questions." They also generally suggested that FDA should not stratify medical devices by technology, but instead should use a risk-based approach and use literature to determine if there are different questions of safety and effectiveness. Comments also suggested that devices of critical importance to health that present evaluation issues that are not common to legally marketed devices with the same intended uses should not be evaluated through the 510(k) or de novo process, but rather through a PMA.

Q4a. Appropriate Comparison Studies. FDA requested comment on when different types of comparison studies would be appropriate for a device under review. Comments discussed generally the circumstances in which certain comparisons may be appropriate. The majority of comments noted that

[197] 21 USC §360c(i).

the type of data needed to support a substantial equivalence determination will be based on the risk and complexity of the device. The comments nearly universally recommended that conformance to a standard should be the first comparison, followed by bench, animal, and clinical data as needed to provide sufficient information regarding the safety and effectiveness of the device. The majority of comments noted that conformance to standards and bench testing will generally be sufficient to demonstrate substantial equivalence, and that clinical trials should only be required if other data are insufficient to demonstrate safety and effectiveness.

Q4b. Clinical Studies. Comments generally stated that large clinical studies would not be necessary for most 510(k)s. Given the nature of devices, numerous comments noted that in many cases bench studies can provide more and better information regarding device safety and effectiveness, although clinical data may be needed to confirm the bench results in a clinical setting or demonstrate usability of the device.

Q4c. Types of Comparison Testing. FDA requested comment on what circumstances would justify different types of comparison testing (*e.g.*, comparison to a standard, concurrent testing of the new device and the predicate(s), etc.) The majority of comments indicated that when recognized standards exist, and the predicate was previously shown to meet those standards, only the new device needs to be tested to demonstrate conformance with the standard. If the devices have technological differences, the submitter may need to compare the new device to the predicate device to verify common specifications and safety and effectiveness profiles. Comments stated that clinical trials should be very rare, and limited to those circumstances in which bench data is insufficient to answer the substantial equivalence question.

Q5. Engineering and Design Information. Comments generally indicated a desire for FDA development of clearer guidance — particularly product-specific guidance — regarding how much design information a submitter should include in a 510(k). Even comments that stated that FDA has provided sufficiently clear guidance on the engineering and design information recognized that submitters would nevertheless appreciate additional guidance to provide clarity and predictability.

Q6. Provisions of the FDCA Unrelated to an SE Decision. FDA requested comment on whether or not it would be beneficial for the agency to have greater authority to withhold an initial classification determination based on failure to comply with current good manufacturing practice (cGMP) requirements or other provisions of the FDCA. The majority of comments did not support increasing FDA's authority to withhold an initial classification determination based on a failure to comply with such provisions. One commenter stated that it is aware of at least one circumstance in which a reviewer did withhold an initial classification based on a failure to comply with a provision of the FDCA unrelated to the substantial equivalence determination, and suggested that FDA management appropriately educate reviewers about the limits of their authority in such circumstances. Other comments noted that FDA's Office of Compliance and other enforcement authorities provide FDA sufficient means to address cGMPs without considering them in the 510(k) process.

A small number of comments noted that failure to conduct pre-clearance inspections may result in FDA being unable to identify certain manufacturing processes that may affect the safety or effectiveness of the device.

Q7. Clinical Utility. FDA requested comment on whether or not it should be a requirement of the 510(k) program that a device's "indication for use" be proven to provide clinical utility. Most comments

were against requiring clinical utility in order to clear medical devices. Reasons cited included: the inability to objectively define "clinical utility;" the unfair burden that would be imposed on new devices that are compared to predicate devices currently on the market; the concern that this borders on FDA regulating the practice of medicine; the difficulty such a requirement would present for devices with multiple purposes or functions; and the position that the marketplace, not FDA, should decide the viability and usefulness of the device upon clearance. Some comments recommended that clinical utility not be required for class I devices or that a risk-based model be used. Of those who supported the need to demonstrate clinical utility, comments noted that FDA needs to strengthen its ability to address obvious off-label use; others suggested that a requirement to demonstrate clinical utility be reserved for novel devices only; others suggested that the intended use statement that is cleared with the device be made more comprehensive. Most responders felt that most devices had obvious clinical uses and did not need to have their clinical utility stated or proven.

Q8. Off-Label Use. FDA requested comment on the effectiveness of its current implementation of section 513(i)(1)(E) of the FDCA[198] with respect to curbing off-label use that could cause harm. The comments uniformly recognized that off-label use by the medical community occurs, and most stated that FDA should not change the 510(k) program to encroach on this (presumably, no matter how common the off-label use is). In fact, the vast majority of comments stated that off-label use is a postmarket issue, and that FDA needs to take stronger enforcement action against 510(k) holders who market their product for off-label uses. Further, a few comments stated that there should be no burden on the companies to conduct premarket studies to address off-label use. On the other hand, a few comments found the current program to be insufficient with respect to off-label use and suggested general changes.

C. Issues Related to Practices CDRH has Adopted in Response to a High Volume of 510(k) Submissions

Third-Party Review Program. Several comments noted problems with the third-party review program and expressed concern about continued use of this system. They suggested that FDA review the current problems with the program and determine whether to make wholesale changes to the program or to eliminate it completely. Several other comments, however, indicated that the third-party review program is beneficial and has been effective in reducing the review burden for CDRH.

Reliance on Declarations of Conformity to Standards/Abbreviated 510(k)s. Comments generally supported CDRH's continued use of standards through the abbreviated 510(k) pathway, and recommended increased communication with industry regarding standards and conformity therewith. Some comments noted that, due to the criminal penalties associated with making false certifications and FDA's ability to confirm the data underlying a certification, certifications of conformance to standards are likely to be truthful.

Reliance on a Single Reviewer. Comments expressed mixed thoughts regarding use of a single reviewer to review each 510(k), noting that there cannot be a "one size fits all approach," and that FDA should prioritize its review resources based on the particular 510(k). Some 510(k)s may more appropriately be reviewed by a single reviewer, while others will require multi-disciplinary review (*e.g.*, more complex devices).

[198] 21 USC §360c(i)(1)(E).

Reasons cited against relying on a single reviewer included the problems that may arise if the reviewer leaves CDRH prior to completing the review, or if the reviewer does not have the necessary technical knowledge or expertise. Furthermore, use of single reviewers may lead to inconsistencies in clearance requirements for similar devices.

Other comments noted that an advantage to a single reviewer is the ability for the review and the 510(k) submitter to interact and discuss issues related to the clearance. This commenter noted, however, that this works well with more seasoned reviewers, but less so with newer, less experienced reviewers.

Special 510(k)s. Comments generally expressed support for the Special 510(k) program, and feel that it is working well to save both industry and FDA resources. Comments also noted that the abbreviated review time for Special 510(k)s incentivizes this pathway. A small number of comments indicated a need for further guidance on the types of applications that may be reviewed through the Special 510(k) pathway, and verification as to the types of information reviewers may request when considering a Special 510(k).

Bundling. Comments generally supported use of bundling, although they acknowledged that more clarity is needed around how and when bundling is appropriate, and that FDA must assure that bundling is implemented and administered in a reasonable and consistent manner. Nevertheless, the comments indicated that bundling can increase consistency and allow FDA to use its resources more effectively. Notably, the comments reflected confusion between a classic bundled submission and complex products such as multiplex devices, which are not bundled submissions. Numerous comments also mentioned the need for FDA to better identify both bundled submissions and multiplex devices after clearance, perhaps by listing all related product codes for these devices. Additionally, comments supported extending the review timeframe for bundled submissions.

D. Issues Related to Postmarket Surveillance and New Information about Marketed Devices

Q1. Condition-of-Clearance Studies. The majority of comments did not support the ordering of postmarket studies as a condition of 510(k) clearance. These comments generally noted that FDA has sufficient postmarket authority under section 522 of the FDCA,[199] through the Medical Device Reporting requirements, and the Quality Systems Regulations. Even the majority of comments that did support postmarket study requirements only did so in limited circumstances, for instance, for devices that, although substantially equivalent to a predicate device, nevertheless raise certain questions of safety or effectiveness at the time of clearance for which postmarket studies are the only means to address those concerns. Comments suggested that if FDA were to take this approach, it should issue guidance discussing the types of devices and circumstances in which a device may be subject to such a requirement. One comment noted that this requirement might be useful for novel medical devices cleared through the 510(k) process.

A small number of comments expressed their desire for FDA to require postmarket studies in all cases as a means of assuring device safety, particularly for devices meant to be used over a long period of time.

Q2. 510(k) Rescission. Numerous comments supported providing FDA with authority to rescind 510(k) clearances, although the majority support doing so only in limited circumstances, generally those in which the device poses a danger to public health or where FDA determines that there have been fraudulent misrepresentations, inaccuracies, or irregularities in the original submission process. Some

[199] 21 USC §360I.

comments noted that FDA has the authority to ban devices and order mandatory device recalls, and these comments stated that FDA's postmarket authority is sufficient to remove devices from the market that present a serious adverse risk to public health and safety. Other comments, however, stated that if FDA determines the device, once marketed, is not as safe and effective as thought when cleared, FDA should have the authority to not only recall the device but also to rescind the clearance. Many comments also noted that if FDA has increased rescission authority, it will need to determine that the issue requiring rescission is related to the design of the device itself and is not a good manufacturing practice issue.

Q3. Use of Postmarket Information in Premarket Review. Although many comments supported the idea of FDA using some postmarket information in the 510(k) clearance process, they recognized the challenges FDA would face in doing so, particularly to determine whether the postmarket information is specific to a particular manufacturer or would have implications for all similar device types. These comments generally suggested that if FDA is aware of postmarket information that could affect a particular device, FDA should communicate this information to the 510(k) submitter and allow the submitter time to address the issues. Comments recommended that if the manufacturer is able to address the issues raised by FDA, the postmarket information should not affect the 510(k) clearance. Many comments also discussed the need for a robust, more user-friendly, adverse events database to make it easier for providers to report adverse events and thus for future 510(k) submitters to be aware of any possible postmarket challenges with a particular device, and to address these concerns in the 510(k). Other comments suggested FDA incorporate known device issues in applicable guidance documents so that 510(k) submitters can address the issues in future device designs.

Q4. Final Device Labeling. A minority of comments suggested that FDA maintain a database of final device labeling or require the inclusion of final labeling in a 510(k) submission. Other comments noted that labeling is often not final until after FDA clears the device since FDA may advise changes to the proposed labeling, and therefore FDA should request final labeling as part of another process, such as listing. The majority of comments, however, indicated that FDA should not require or review the submission of final device labeling. The reasons given for not requiring final labeling included: the clearance letters describe the cleared indications for use and intended use, and any change to those aspects of labeling are evident when a submitter files a new 510(k) for a labeling change; FDA should use its postmarket authorities to assure that labeling is appropriate relative to cleared language; and draft labeling generally adequately represents the final labeling. Furthermore, comments noted that the 510(k) may be submitted well in advance of product launch, and since final product labeling is generally a last deliverable prior to launch, the requirement to submit final product labeling to FDA could unnecessarily delay the launch. One comment suggested that FDA should have the authority to require final labeling only in cases where claims or instructions for use are critical to the clearance decision or if the manufacturer has a history of inappropriately modifying device labeling.

Q5. Purchase, Sale, or Transfer of 510(k) Ownership. The vast majority of comments supported FDA exercising its authority to require information about the purchase, sale, or transfer of 510(k) ownership. Numerous comments suggested FDA enhance the current database to link the device listing database to the 510(k) database, and encouraged FDA to issue guidance on reporting transfers of 510(k) ownership so that companies are aware of the processes to follow.

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APPENDIX D: REVIEWER SURVEY

To assess the consistency of CDRH reviewers' interpretation and understanding of 510(k) regulations, guidance documents, and review practices, the Working Group conducted a survey of the Center's premarket reviewers and managers. The survey consisted of twenty questions related to reviewers' and managers' knowledge and opinions on a range of identified areas of concern, including many of the subgroup topics listed in Section 3.1 of this report.

Reviewer Cohort. The survey was sent by email to all reviewers in CDRH's two premarket review Offices, the Office of Device Evaluation (ODE) and the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), and all reviewers were strongly encouraged to complete it. Out of a total of 308 reviewers, 215 reviewers took the survey, and at least 162 respondents answered each question.

Manager Cohort. Premarket review managers in ODE and OIVD also completed the survey as a separate cohort of respondents. Premarket review managers also completed the survey as a separate cohort of respondents. Out of a total of 38 managers (Branch Chiefs, Deputy Division Directors, and Division Directors) in ODE and OIVD, 21 ODE Branch Chiefs and Deputy Division Directors took the survey, and at least 13 respondents answered each question.

This Appendix provides a full listing of the survey questions and responses. Correct responses, where they exist, are listed in **bold**. For each question, "% Selected" indicates the percentage of respondents who selected a given option, among those respondents who answered that question. Note that some respondents skipped questions; therefore the total number of respondents who answered each question varies. Percentages may not sum to 100 percent due to rounding.

Question 1: In reviewing a 510(k) application, you may find the device substantially equivalent to a predicate device when the device under review has a new intended use and:

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. The same technology.	6.7% (14)	0.0% (0)
B. The same technology and appropriate bench testing.	5.2% (11)	4.8% (1)
C. The same technology and appropriate bench and clinical testing.	28.1% (59)	14.3% (3)
D. You cannot find this device SE.	**60.0% (126)**	**81.0% (17)**

Question 2: In reviewing a laser 510(k) application, the predicate device was cleared for skin resurfacing and the new device would like to add wrinkle removal in conjunction with skin resurfacing. The reviewer has determined that there are no differences in therapeutic effect; therefore this represents:

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. A new indication.	18.2% (37)	15.0% (3)
B. A new intended use.	15.3% (31)	5.0% (1)
C. The same intended use.	10.8% (22)	15.0% (3)
D. Both (A) and (C).	**55.7% (113)**	**65.0% (13)**

Question 3: In determining the intended use of the device, you would look at:

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. The Indications for Use (IFU) form.	1.0% (2)	0.0% (0)
B. Labeling submitted by the firm.	1.5% (3)	0.0% (0)
C. Statements made in the file or specific design attributes of the device.	1.0% (2)	0.0% (0)
D. Predicate device labeling.	1.0% (2)	0.0% (0)
E. (A), (B), and (C).	**95.6% (196)**	**100.0% (21)**

EMBARGOED

Question 4: You have a 510(k) under review that has the same indication for use as the predicate but involves a new technology. While most of the information provided in the 510(k) is consistent with the specified indication for use, you find a reference to an indication that suggests a new intended use. You further investigate this issue by performing a cursory review of the literature and the MDRs. You discover that this type of device is being used by the medical community primarily for this new use. You have safety concerns about how this technology can be used for this new use but not for the labeled use. The sponsor has clearly stated that the device has the same intended use as the predicate, and the labeling has no reference to this new intended use. What decision should FDA make?

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Issue an SE decision based on the proposed labeling in the 510(k) that is silent on the new intended use.	5.5% (11)	0.0% (0)
B. Require the sponsor to add a black box warning against the new intended use of the device in the labeling before issuing an SE decision.	24.9% (50)	28.6% (6)
C. Follow the SE with Limitations process.	**49.8% (100)**	**61.9% (13)**
D. Issue an NSE decision because of how these types of devices are being used in the medical community (*i.e.*, new intended use) and you have significant doubts that the sponsor truly intends to market it for the indications they are seeking.	19.9% (40)	9.5% (2)

Question 5: When you have a different indication for use and are trying to assess whether this presents a new intended use, what information do you consider to determine if there is a new intended use that would result in an NSE decision?

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. I would need to ask the sponsor to provide clinical data to assess the differences before I can determine.	0.0% (0)	0.0% (0)
B. I would consider whether the device has a new therapeutic or diagnostic effect.	9.8% (20)	14.3% (3)
C. I would consider whether the indication raises new safety and/or effectiveness issues.	5.4% (11)	0.0% (0)
D. (B) and (C).	**54.9% (112)**	**52.4% (11)**
E. (A), (B), and (C).	29.9% (61)	33.3% (7)

Question 6: When reviewing a 510(k) for a modification to a predicate device, you need to determine which path to take on the flowchart. For the examples below, assume that the indications for use are unchanged and you get to the section of the flowchart that states, "Does New Device Have Same Technological Characteristics?" Which of the following represent a change in the technological characteristics from the predicate device to the subject device? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Replacing a digital x-ray detector's wired network connection with a wireless one.	**83.5% (157)**	**95.2% (20)**
B. Changing a catheter's material from silicone to polyvinyl chloride (PVC).	**75.0% (141)**	**76.2% (16)**
C. Moving a warning label from the back of an automated external defibrillator (AED) to the front of the device.	1.6% (3)	0.00% (0)
D. Adding an emergency stop button to a device.	**51.1% (96)**	**42.9% (9)**
E. A manufacturer of a central venous catheter that is sold to a distributor submits a 510(k) for the same product.	2.7% (5)	0.0% (0)
F. Updating the software in a device to run on Windows 7 instead of Windows XP.	**50.0% (94)**	**38.1% (8)**
G. Changing the recommended sterilization method for a device.	**50.0% (94)**	**57.1% (12)**
H. Adding a coating to inhibit the growth of microorganisms on the surface of the device.	**93.1% (175)**	**85.7% (18)**
I. Adding a signal processing algorithm to assess brain wave activity to an electroencephalograph (EEG).	**89.9% (169)**	**90.5% (19)**

EMBARGOED

Question 7: Once you have identified that the subject device has the same intended use and different technological characteristics that could affect the safety or effectiveness of the device, you have to determine if those technological characteristics raise any new types of questions of safety or effectiveness. Which of the examples below represent a new type of safety or effectiveness question(s)? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. An ultrasound device cleared for imaging of a fetus has a new feature to assess the stiffness of coronary arteries to determine if there is coronary artery disease.	**87.0% (160)**	**85.7% (18)**
B. A surgical device cleared to cut and ablate tissue using RF (radiofrequency ablation) is the predicate for a microwave thermotherapy system to necrose tissue.	**71.2% (131)**	**52.4% (11)**
C. A manual medical device such as a colonoscope is redesigned to be fully automated.	**78.3% (144)**	**38.1% (8)**
D. A class I medical device exempt from premarket notification requirements where the sponsor intends to coat this device with a drug to reduce inflammation.	**91.8% (169)**	**90.5% (19)**
E. A roller cardiopulmonary bypass blood pump (a device that uses a revolving roller mechanism to pump the blood during cardiopulmonary bypass surgery) is modified to use a centrifugal pump that uses centrifugal force to control blood flow.	59.8% (110)	47.6% (10)
F. A battery-operated powered wheelchair cleared to provide mobility to persons restricted to a sitting position is modified to add a stair-climbing capability.	**79.9% (147)**	**52.4% (11)**

Question 8: Regarding the 510(k) "Substantial Equivalence" Decision-Making Process flowchart, how difficult is it for you to make the determination that the new technological characteristics raise new types of safety or effectiveness questions?

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Very difficult.	14.9% (28)	19.1% (4)
B. Somewhat difficult.	26.1% (49)	23.8% (5)
C. Occasionally difficult.	43.1% (81)	47.6% (10)
D. Rarely difficult.	16.0% (30)	9.5% (2)

Question 9: What percentage of the time did you find it moderately or highly difficult to obtain the studies (performance, animal, or clinical) that were necessary for you to make your SE/NSE decision?

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. Less than 10%.	21.1% (39)	42.9% (9)
B. Between 11-25%.	31.4% (58)	14.3% (3)
C. Between 26-50%.	25.4% (47)	28.6% (6)
D. Between 51-75%.	14.6% (27)	9.5% (2)
E. Greater than 75%.	7.6% (14)	4.8% (1)

Question 10: Consider the following 510(k) scenario. A sponsor submits a 510(k) seeking clearance for "Device X." It is the same device type and has the same indications and intended use as "Predicate A," but there are differences in technological characteristics between proposed "Device X" and "Predicate A," and these technological differences could affect safety or effectiveness. Ordinarily, the next steps in the 510(k) decision-making process would be to determine whether the technological differences raise new types of safety or effectiveness questions, and, if the answer is no, to evaluate performance data to assess the impact of the technological differences. However, in this 510(k), the sponsor has also identified a second predicate device, "Predicate B." This predicate is a different device type but the technological characteristics are the same as the proposed device. If you were the reviewer of this 510(k), which predicate device(s) would you use when making your SE/NSE determination for "Device X"?

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. "Predicate A" only, because it has the same intended use.	**34.4% (64)**	**45.0% (9)**
B. "Predicate A" for the intended use, and "Predicate B" for the technological comparison.	33.9% (63)	20.0% (4)
C. "Predicate B" only, because it has the same technological characteristics.	3.8% (7)	0.0% (0)
D. Neither predicate, because the sponsor needs to identify a different predicate device that has the same intended use and the same technological characteristics.	28.0% (52)	35.0% (7)

EMBARGOED

Question 11: The Awesomo device was cleared with general indications and labeling that do not specify an age range for the intended patient population or whether the device is for use in a clinical setting or at home. Which of the following changes would require a new 510(k)?

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. A revision of the labeling that specifies the device can be used for both adults and children.	1.1% (2)	9.5% (2)
B. A revision of the labeling that specifies the device can be used by a patient at home (by prescription use only).	1.6% (3)	9.5% (2)
C. A revision of the labeling that specifies the device can treat certain medical conditions.	7.5% (14)	19.0% (4)
D. All of the above.	**73.1% (136)**	**66.7% (14)**
E. (A) and (C).	16.7% (31)	19.1% (4)

Question 12: Which of the following technological device modifications could result in a new 510(k)? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Extension of shelf life from 1 year to 5 years using methods described in the original 510(k).	40.1% (75)	14.3% (3)
B. Addition of a wireless communication feature.	**94.7% (177)**	**95.2% (20)**
C. Change from AC to battery power.	**70.6% (132)**	**61.9% (13)**
D. Dimensional specification changes.	**56.2% (105)**	**47.6% (10)**
E. Change in sterilization from gamma irradiation to ethylene oxide sterilization, with the same SAL (the material is not affected by the new sterilization method).	**55.1% (103)**	**66.7% (14)**

EMBARGOED

Question 13: Which submissions can be bundled? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Submissions that require only one set of data (*i.e.*, same intended use population).	**82.7% (139)**	**95.2% (20)**
B. Submissions describing a similar change >200 reprocessed devices.	**39.9% (67)**	**47.6% (10)**
C. Submissions for bedside monitors that include a number of parameters, for example heart rate, arrhythmia detection, and exercise equipment.	**47.0% (79)**	**52.4% (11)**
D. Submissions with different IFUs and populations, for procedures on different body parts.	5.4% (9)	0.0% (0)
E. Submissions that require review by several different divisions.	6.0% (10)	4.8% (1)

Question 14: What is a "bundled device" ("system")? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Device that consists of several different devices which are physically inter-connected.	**67.9% (114)**	**61.9% (13)**
B. Networked devices.	37.5% (63)	23.8% (5)
C. One submission for multiple devices with the same change across a number of similar devices.	39.9% (67)	33.3% (7)
D. Device that can contain inter-connected diagnostic and therapeutic parts.	**56.0% (94)**	**57.1% (12)**

EMBARGOED

Question 15: What constitutes a bundled submission but is not a bundled device ("system")? (Select all that apply.)

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. Multiple devices with the same change across a number of similar devices.	**72.8% (118)**	**76.2% (16)**
B. A number of similarly designed dental implants.	49.4% (80)	52.4% (11)
C. Multiplex assay for 40 different analytes.	25.3% (41)	23.8% (5)
D. Assay for 20 different allergens that need data from the same patient population.	40.7% (66)	42.9% (9)
E. Bedside monitors that include a number of parameters, for example heart rate, arrhythmia detection, and exercise equipment.	21.0% (34)	19.1% (4)

Question 16: Which of the following devices is NOT eligible for the de novo process? (Assume there are not any unmentioned factors that make them ineligible for de novo.)

Option	**Reviewers** % Selected (#)	**Managers** % Selected (#)
A. A device that already has a valid predicate.	13.6% (24)	19.1% (4)
B. A device that has been classified into class III by regulation.	7.3% (13)	9.5% (2)
C. A low-risk device for which there is no valid predicate.	9.6% (17)	4.8% (1)
D. (A) and (B) only.	**69.5% (123)**	**85.7% (18)**

EMBARGOED

Question 17: Which of the following are examples of special controls? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Guidance document.	**83.1% (147)**	**95.2% (20)**
B. Postmarket study.	**49.7% (88)**	**42.9% (9)**
C. Patient registries.	**42.4% (75)**	**38.1% (8)**
D. Medical Device Reporting (MDR).	26.6% (47)	38.1% (8)
E. Good Manufacturing Practices.	32.8% (58)	57.1% (12)
F. Standards.	**69.5% (123)**	**80.1% (17)**
G. Device labeling recommendations.	**68.4% (121)**	**90.5% (19)**

Question 18: A 510(k) submission typically is not eligible for third-party review if it:

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Is for a class II device that requires clinical data.	**59.9% (103)**	**92.9% (13)**
B. Is for a class I device that presents significant risk.	3.5% (6)	0.0% (0)
C. Is a Special 510(k) rather than a Traditional or Abbreviated 510(k).	8.7% (15)	0.0% (0)
D. Is for a class II device, and FDA has not issued device-specific guidance.	27.9% (48)	7.1% (1)

EMBARGOED

Question 19: According to FDA's guidance on third-party review, which of the following statements is true?

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. Third parties normally should perform an independent review without contacting FDA for guidance.	6.5% (11)	5.0% (1)
B. Third parties should access FDA's IMAGE system to view 510(k)s for predicate devices.	3.5% (6)	0.0% (0)
C. If a third party identifies any deficiencies in a 510(k) submission, the third party should contact the 510(k) submitter.	**20.0% (34)**	**40.0% (8)**
D. Both (A) and (C).	70.0% (119)	60.0% (12)

Question 20: Which of the following items do you believe you have the authority to use to support your premarket review? (Select all that apply.)

Option	Reviewers % Selected (#)	Managers % Selected (#)
A. MDRs.	**95.1% (175)**	**100% (21)**
B. Recalls.	**89.1% (164)**	**95.2% (20)**
C. Network signals.[200]	**73.4% (135)**	**85.7% (18)**
D. Literature.	**95.7% (176)**	**95.2% (20)**

[200] "Network signals" refer to information from various parts of the Center that raise questions about the safety and/or effectiveness of a specific device or device type.