

## FDA Begins Overhaul of the 510(k) Process

The US Food and Drug Administration (FDA) recently released the preliminary results of an internal study aimed at improving one of its major pathways for premarket review of medical devices—the “510(k)” premarket notification process. Both within and outside the Agency, the 510(k) process has been criticized as unpredictable, insufficiently adaptive to changes in technology, and inconsistently applied. The process has come under increasing scrutiny in the last few years, especially after the Agency’s much-criticized 510(k) clearance, in December 2008, of ReGen Biologics Inc.’s collagen scaffold device for meniscal repair, followed by initiation of a “re-review” of this product in the summer of 2009.<sup>1</sup> To address these and other concerns, in September 2009 FDA’s Center for Devices and Radiological Health (CDRH or the Center) launched an extensive internal review of the 510(k) process and commissioned the Institute of Medicine (IOM) to evaluate it as well.<sup>2</sup> Collectively, these recommendations, if implemented, have the potential to radically alter the 510(k) process as we know it today.

On August 4, 2010, CDRH released two preliminary reports from its internal review: “CDRH Preliminary Evaluations—Volume 1: 510(k) Working Group Preliminary Report and Recommendations” and “CDRH Preliminary Evaluations—Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations.”<sup>3</sup> These reports contain recommendations on how CDRH can improve its decision-making in this area. Following, we summarize the recommendations in each report.

FDA is accepting public comments on these reports through October 4, 2010. After FDA has assessed the comments, particularly those concerning feasibility of implementation and potential alternatives, it will announce which improvements it will seek to pursue. FDA may implement some of these changes through new or revised guidance documents,

<sup>1</sup> See FDA’s Preliminary Report, “Review of the ReGen Menaflex: Departures from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question” (Sept. 2009), available at: <http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM183642.pdf>.

<sup>2</sup> See FDA press release, “Institute of Medicine to Study Premarket Clearance Process for Medical Devices” (Sept. 23, 2009), available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm183497.htm>.

<sup>3</sup> See reports on FDA’s website available at: <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm220272.htm>.

### Contacts



**Daniel A. Kracov**  
+1 202.942.5120



**Vernessa T. Pollard**  
+1 202.942.5811



**Thomas A. Gustafson**  
+1 202.942.6570

others through proposed rulemakings, and still others through seeking statutory amendments.

The IOM's study of the 510(k) process is estimated to conclude in the summer of 2011. Whereas FDA's internal review focuses primarily on changes that can be made within existing statutory authorities—or identifying areas where more authority may be needed—the IOM was given an apparently broader mandate, possibly to reconceptualize the 510(k) process. The two principal questions that FDA posed to the IOM were: (i) Does the current 510(k) process optimally protect patients and promote innovation in support of public health?; and (ii) If not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) process? Given this broader mandate, it is likely that the IOM report, when issued, will contain more recommendations for statutory changes than do the recently issued CDRH reports. If and when FDA seeks statutory amendments to the 510(k) process, it will likely do so as part of seeking reauthorization from Congress for medical device user fees for fiscal year (FY) 2013 and beyond.

### Volume I: 510(k) Working Group

The 510(k) Working Group, comprised of CDRH reviewers and managers and others within FDA, was charged with evaluating the 510(k) program and exploring actions that CDRH could take to strengthen the program and improve the consistency of its decision-making, focusing primarily on changes the Center could make under its existing statutory authority. The Working Group gathered input from FDA employees and external constituencies, and reviewed past submission data to identify pre-market and post-market trends.

### Regulatory Background

FDA classifies medical devices into three categories according to their level of risk. Class I and Class II devices pose lower risks and include devices such as adhesive bandages, wheelchairs, some types of diagnostic devices, and some types of infusion pumps. Most Class II devices and some Class I devices must obtain clearance from FDA prior to marketing, through submission of

premarket notifications—called 510(k) submissions. These submissions must demonstrate to FDA that the device is “substantially equivalent” to a legally marketed predicate device, often without including any clinical data. Class III devices represent the highest level of risk and include heart valves and intraocular lenses. Class III devices generally require premarket approval (PMA) demonstrating their safety and effectiveness, which is a more stringent and lengthy process than the 510(k) “substantial equivalence” review.

“Substantial equivalence” is a term defined by statute. Under Section 513(i) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 360c(i),

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 the Secretary has by order 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 the Secretary 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 issues of safety and effectiveness than the predicate device.*

FDCA § 513(i), 21 U.S.C. § 360c(i) (emphases added).

Among its main findings, the 510(k) Working Group found that key terms in the statutory and regulatory definition of “substantial equivalence” have not been consistently interpreted by CDRH, in particular what constitutes the same versus a new “intended use,” how “indications for use” relate to “intended use,” and when “different

technological characteristics” raise “different questions of safety and effectiveness.” Other concerns identified include the use of so called “split predicates,” or using one predicate as the basis for comparing intended use and another as the basis for comparing technological characteristics, and the need for clarity on evidentiary expectations for 510(k) submissions.

### **Recommendations for Enhancing Regulatory Clarity and Predictability**

The 510(k) Working Group recommends that CDRH clarify the meaning of “substantial equivalence” to alleviate ambiguity arising from multiple references to key definitional terms in the FDCA, FDA regulations, and FDA guidance documents, which give rise to inconsistencies in interpretation and application. Clarity is needed, in particular, on the meaning of “intended use” (and its relation to “indications for use”), “different technological characteristics,” and “different questions of safety and effectiveness.”

On “intended use,” the 510(k) Working Group recommends consolidating the concepts of “indication for use” and “intended use” into a single term, “intended use.” Under CDRH’s current policy, it is generally understood that “indications for use” is a narrower term than “intended use”: not all changes to “indications for use” may result in a change to “intended use.” In recommending consolidation of these terms, the Working Group explains that its aim is not to make the concept of “intended use” more restrictive, but rather to provide “greater clarity and simplicity.” Thus, the Working Group advises CDRH to “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”—not also changes in “intended use”—do not automatically result in a new “intended use,” merely because of “a change in semantics.” The Working Group further advises that CDRH develop guidance identifying relevant criteria and provide training on how to evaluate other key elements of “substantial equivalence,” namely “different technological characteristics” and “different questions of safety and effectiveness.” One of the guidance documents the Working

Group recommends is a document delineating a “core list” of technological characteristics that generally raise different questions of safety and effectiveness.

Further clarity is needed on the use of more than one predicate, according to the Working Group. The Working Group identified “differences of opinion” among CDRH’s review staff on the validity of using “split predicates,” or using one predicate as the basis for comparing intended use and another as the basis for comparing technological characteristics. This concept is distinct from “multiple predicates” for so-called “combination devices” that combine two predicates into one device, such as multi-parameter monitors (e.g., a urinary catheter that incorporates a temperature measuring device). As described by the Working Group, “split predicates” are unlike “multiple predicates” in that they do not represent a simple aggregation or consolidation of device features and functionality into one device; rather, they represent the creation of an entirely new device that may “bear little resemblance” to the device under review. A concern with “split predicates” is that they may not allow valid comparisons of safety and effectiveness, because there is no “real-world information” about risks and benefits of the device under review. The Working Group advises that CDRH explore the possibility of expressly disallowing the use of “split predicates,” or alternatively provide guidance to industry and better training to reviewers and managers about how to use and analyze more than one predicate. The Working Group further recommends that CDRH determine the basis for the “apparent association between [devices cleared through reliance on] more than five predicates and a greater mean rate of adverse events.”

The Working Group also considered off-label use of devices under 510(k) review. Under the current regulatory scheme, the primary means by which CDRH addresses anticipated off-label use is through requiring, as a condition of clearance in certain circumstances, a statement in the labeling with appropriate information on off-label use (e.g., a warning). FDCA § 513(i)(1)(E), 21 U.S.C. § 360c(i)(1)(E). This process is often referred to as a “substantial equivalence with limitations” decision. The Working Group reports that

this provision is often difficult to implement and may not provide sufficient protection against potentially harmful off-label use.<sup>4</sup> The Working Group recommends that CDRH consider pursuing alternate means to protect against off-label use when there is reason to believe that the device's primary "intended use" will be off-label. An amendment to Section 513(i)(1)(E) of the FDCA, 21 U.S.C. § 360c(i)(i)(E), could give CDRH express authority to consider off-label use during 510(k) review, and guidance from CDRH could define what type and level of evidence would suffice for CDRH to designate off-label use as the "primary" intended use for purposes of review and clearance.

### **Recommendations for Enhancing Data Quality and Ensuring Well-Informed Decision-Making**

The 510(k) Working Group recommends that CDRH develop guidelines to define higher risk devices ("class IIb devices") for which additional clinical, manufacturing, and/or other information may be required in a submission to support a substantial equivalence determination. The Working Group makes clear that delineating between "class IIa" and "class IIb" devices would not reconfigure the current statutory three-tier classification scheme (Class I, Class II, and Class III devices), but would instead represent an "administrative distinction" for purposes of evidentiary expectations for 510(k) submissions. Suggested devices in this class would include implantable devices, life-sustaining devices, and/or life-supporting devices. A device could be transferred to the "class IIa" from the "class IIb" subset as its technology and risk/benefit profile in clinical practice become better understood. Related recommendations include that CDRH define the type and level of clinical data that would typically be necessary to support substantial equivalence for this subset of "class IIb" devices.

The Working Group further recommends that CDRH explore the feasibility of requiring device manufacturers to provide regular, periodic updates listing any modifications

made to devices without a new 510(k) and explaining why each such modification did not warrant a new 510(k). This recommendation would allow CDRH to monitor and assess incremental or "minor" device changes that, under current policy, CDRH may learn of only years later, through subsequent 510(k) submissions for "major" changes or through site inspections. The Working Group recommends phasing in this suggested requirement, applying it initially to the "class IIb" subset of devices and then expanding its applicability to other devices.

Another recommendation is for CDRH to adopt an "assurance case" framework for 510(k) submissions, which may enhance the clarity and reliability of information included in a 510(k). The Working Group describes an assurance case as "a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence." Assurance cases are further described in a recent FDA Draft Guidance on Infusion Pump 510(k) Submissions (April 23, 2010).<sup>5</sup>

### **Recommendations on Fostering Innovation**

The 510(k) Working Group recommends reforms to streamline and clarify the process for "de novo" classification, a process for classifying lower-risk novel devices that are not well-suited to the 510(k) review process because they lack a clear predicate but whose risks do not warrant a PMA approach. FDCA § 513(f)(2), 21 U.S.C. § 360c(f)(2). Added by Congress in 1997, the de novo classification was meant to remove lower risk devices from unnecessarily burdensome PMA review but also prevent attempts to "force" substantial equivalence by relying on "remote predicates." The Working Group reports that the de novo process is used for only a small number of devices and can be very time-consuming, as the process often takes many review cycles and CDRH typically develops device-specific guidance with each de novo classification to serve as "special controls" for the device (a statutory term of art). The Working Group recommends that CDRH establish a general set of controls

<sup>4</sup> CDRH has authority to engage in rulemaking to restrict the sale, distribution, or use of a 510(k)-cleared device, and thereby control off-label use, but as the Working Group reports this process can take years to complete and is rarely employed. FDCA § 520(e), 21 U.S.C. § 360j(e).

<sup>5</sup> This draft guidance is available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm206153.htm>.



that could serve as baseline “special controls” for these de novo devices, to be supplemented as needed with device-specific guidance. The Working Group also advises that CDRH convey to manufacturers early in the review process if their devices may be eligible for de novo classification, and if so what type of data and other evidence FDA would expect to see in a de novo classification request.

### **Other Recommendations Concerning Post-Market Authorities, Patient Safety, and Public Availability of Information**

The Working Group made a number of other recommendations for improving the 510(k) review process, including:

- Exploring greater use of post-market authorities to require studies as a condition of clearance beyond the authority currently available under Section 522 of the FDCA, 21 U.S.C. § 360I;
- Considering issuing a regulation to define CDRH’s authority and procedures to rescind 510(k) clearance (essentially reviving a rescission rule proposed in 2001 that FDA never finalized<sup>6</sup>), and whether additional statutory rescission authority is needed;
- Changing existing regulations to expressly require 510(k) submissions to include a summary of all scientific information regarding the safety and effectiveness of the device known to, or that should be reasonably known to, the submitter (rather than just the information relied on to support substantial equivalence);
- Exploring the feasibility of requiring manufacturers to electronically submit final device labeling to FDA by the time of clearance or within a reasonable time thereafter, and to provide FDA with regular updates of device labeling, perhaps as part of annual registration and listing;

<sup>6</sup> A copy of this proposed rule is available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/oc94190.pdf>. FDA stated in this proposed rule that, pending completion of such a rulemaking, FDA would only rescind, or propose to rescind, substantial equivalence orders in cases involving: (i) a serious adverse risk to public health or safety; (ii) data integrity or fraud; or (iii) other compelling circumstances. Under this policy and as proposed in the 2001 rule, FDA would provide the 510(k) holder with notice and opportunity for a hearing, a procedural protection that the Working Group recommends retaining (and which is likely legally required).

- Expanding and improving on FDA’s publicly available, searchable 510(k) database; and
- Enhancing recruitment, retention, training, and development of review staff.

### **Volume II: Task Force on the Utilization of Science in Regulatory Decision Making**

The second report issued by CDRH, by the Task Force on the Utilization of Science in Regulatory Decision Making, focuses on enhancing CDRH’s scientific knowledge, developing a predictable approach to determine whether and when new scientific information warrants a change in evidentiary expectations, and promptly communicating current or evolving thinking to all affected parties. Among other recommendations, the Task Force recommends:

- Establishing a Center Science Council to provide Center-wide oversight and assure quality and consistency in scientific decision-making across CDRH;
- Developing more guidance on pre-Investigational Device Exemption (IDE) interactions and other pre-submission interactions with FDA, with the aim of improving the quality, design, and performance of clinical trials to support marketing applications;
- Establishing a standard practice of sending uniform “Notice to Industry” letters to all manufacturers of a particular group of devices for which the Center has changed its regulatory expectations on the basis of new scientific information, to be placed in the public docket for public comment and followed where appropriate by new or revised guidance; and
- Expanding the scope of publicly available information about regulated products through the CDRH Transparency Website.

Overall, the Task Force’s aim is to help CDRH become more “predictably adaptive” to new scientific information and to enhance CDRH’s ability to monitor and understand new scientific developments.

It seems clear from these two reports that the 510(k) program will undergo a significant overhaul in the coming months and years. Industry can expect a number of new or revised

# ARNOLD & PORTER LLP

industry-wide and device-specific guidance documents to issue after the conclusion of this review and the IOM's review, as well as proposed regulations where appropriate and requests for statutory amendments. Industry can expect at least some proposals for statutory amendments to be made during renegotiation and reauthorization of medical device use fees for FY 2013 and beyond.

---

*We will be closely monitoring developments in the 510(k) program, and we will issue updates to this advisory as appropriate. If you have any questions, please contact your Arnold & Porter attorney or:*

**Daniel A. Kracov**

+1 202.942.5120

Daniel.Kracov@aporter.com

**Vernessa T. Pollard**

+1 202.942.5811

Vernessa.Pollard@aporter.com

**Thomas A. Gustafson\***

+1 202.942.6570

Tom.Gustafson@aporter.com

**Margaret W. Renner**

+1 202.942.5110

Margaret.Renner@aporter.com

*\* Not admitted to the practice of law.*

*\*\* Special thanks to Deborah Birnbaum for her assistance with this advisory.*

---

© 2010 Arnold & Porter LLP. This advisory is intended to be a general summary of the law and does not constitute legal advice. You should consult with counsel to determine applicable legal requirements in a specific fact situation.