

### **FDA Issues Recommendations on 510(k) Reform and Use of Science in Regulatory Decision Making**

**August 13, 2010**

On August 4, 2010, the Food and Drug Administration (FDA or the Agency) issued its long-awaited recommendations on reform of the 510(k) process. At the same time, it issued a second report including recommendations on how the Agency's Center for Devices and Radiological Health (CDRH) could better use science in its regulatory decision making. The proposed reforms focus on the 510(k) review standard, FDA's decision making on 510(k)s, and the training of FDA staff. While some of the proposed reforms are intended to expedite 510(k) clearance, a number of the recommendations, if implemented, could make it more difficult to obtain clearance, particularly for more innovative devices. Moreover, one or more of FDA's recommendations may jeopardize the current regulatory status of certain cleared devices.

The Agency has stressed that its recommendations are "preliminary," and has titled its report "CDRH Preliminary Internal Evaluations—Volumes I and II." Comments on the two reports are due by October 4, 2010 and can be submitted online to FDA Docket Number FDA-2010-N-0348 at [www.regulations.gov](http://www.regulations.gov). FDA will announce which changes it will implement, and the estimated timelines for implementation, after it reviews the submitted comments. It is expected that some of the changes could be implemented within weeks or months.

The 510(k) process came under heavy criticism in the wake of FDA's controversial review of a 510(k) submission from ReGen Biologics for its Menaflex knee implant, a product that many believed required a premarket approval (PMA) application. Following an internal review of the Menaflex 510(k) controversy, a special FDA team concluded that improvements in the 510(k) process were needed and recommended an independent review of the 510(k) program. Subsequently, in September 2009, CDRH formed a 510(k) Working Group to perform this evaluation. This 510(k) Working Group authored one of the two reports issued on August 4. CDRH also requested that the Institute of Medicine (IOM) conduct an independent study of the 510(k) program. The IOM is expected to issue its report on the 510(k) process in the summer of 2011.

The second report was authored by the Task Force on the Utilization of Science in Regulatory Decision Making (the Task Force), which was formed in September 2009 to review how CDRH uses science in its regulatory decision-making process. The Task Force was also charged with making recommendations on how CDRH could incorporate evolving scientific information, novel technologies, and new scientific

methods into its decision making quickly, while still maintaining the predictability of the review process. The Task Force included representatives from across CDRH.

Overall, the two reports total more than 150 pages and include more than 60 recommendations. We have briefly described below some of the more significant recommendations from each report that may present important issues for device manufacturers and warrant consideration of submission of comments to CDRH.

### **510(k) Working Group: Recommendations to Reform the 510(k) Process**

1. **New class IIb:** Increase the predictability of 510(k) data needs by establishing a new subset of class II devices, called “class IIb,” for which clinical information, manufacturing information, or possible postmarket data would typically be necessary to support a substantial equivalence determination, and develop guidance describing the type and level of clinical data required for clearance.

Although the 510(k) Working Group opined that the creation of a new class IIb was within the scope of the current, three-tiered device classification system established by statute, it is unclear whether FDA has the statutory authority to split the classes into subcategories. The 510(k) Working Group identified as potential candidates for class IIb status implantable, life-sustaining, and/or life-supporting devices, but noted that further consideration by CDRH on the class IIb scope is required. The 510(k) Working Group recommended that CDRH develop and implement training for review staff and industry regarding the delineation between “class IIa” and “class IIb.”

2. **Rescission authority:** Consider issuing a regulation to define the grounds of, and appropriate procedures for, FDA to rescind or partially rescind a 510(k) clearance.

Although rescission is not specifically addressed in the Federal Food, Drug, and Cosmetic Act, FDA’s position is that it has the inherent authority to reconsider decisions where there has been fraud or error, and to rectify its mistakes. FDA previously proposed a rescission regulation in 2001, but never finalized it, possibly due to concerns regarding the extent of FDA’s statutory authority.

3. **Multiple and split predicates:** To provide greater assurance that any comparison of a new device to a predicate is valid and well reasoned, consider (a) issuing guidance on the appropriate use of multiple predicates, and (b) disallowing the use of “split predicates” (i.e., the use of one predicate for “intended use” and another for “technological characteristics”).

The report suggests that 510(k)s citing more than one predicate may be associated with more adverse event reports, but recommends that additional analyses be conducted to evaluate this association. The formal limitation on the use of multiple and split predicates is likely to impact many device companies, particularly those that continually modify their devices. While some CDRH review divisions have already informally limited the use of multiple and split predicates, others continue to allow this practice.

4. **Unreported device modifications:** Revise existing guidance to clarify what types of modifications warrant submission of a new 510(k), and explore requiring manufacturers to

provide periodic updates to CDRH listing any modifications made without submitting a new 510(k).

Implementation of this recommendation would likely substantially increase the number of 510(k)s submitted to FDA. However, the 510(k) Working Group explains that CDRH does not always have sufficient information to evaluate a modified device reported in a 510(k) due to the cumulative effect of unreported modifications that preceded the change identified in the 510(k) submission. Additionally, the 510(k) Working Group notes that manufacturers often misinterpret the regulation to mean that a new 510(k) is required only if a modification could negatively affect safety and/or effectiveness when such submission is also required if a change could positively affect safety and/or effectiveness.

5. **Use of “assurance case” framework:** Consider adopting the use of an “assurance case” framework for 510(k) submissions that requires formal validation of claims with supporting evidence, and explore developing guidance requiring that the complete device description and intended use information be submitted and described in detail in a single section of a 510(k).

The 510(k) Working Group identified the current lack of quality and clarity in 510(k) submissions as a challenge for CDRH reviewers, and recommended an “assurance case” framework to address these issues. The “assurance case” is a way of structuring information and arguments to help ensure that high-level claims are accurate and supported by evidence. Additionally, the 510(k) Working Group recommends that all device description and intended use information be described in detail in a single section of a 510(k).

6. **“Substantial equivalence”:** Clarify in guidance the meaning of certain critical terms in the statutory definition of “substantial equivalence,” including “intended use” and “different questions of safety and effectiveness.”

The current confusion concerning the definitions and distinction of the terms “indications for use” and “intended use” has created difficulty for both industry and FDA reviewers. The 510(k) Working Group recommends that CDRH revise existing guidance to consolidate the concepts of “indications for use” and “intended use” into a single term “intended use.” Additionally, the 510(k) Working Group recommends that existing guidance be revised to clarify what differences in technological characteristics raise “different questions of safety and effectiveness.”

7. **“De novo” process:** Streamline the evaluation of automatic class III designation (i.e., the “de novo” classification) process for lower-risk devices.

The intent of the de novo process was to avoid subjecting unclassified low-risk devices to burdensome PMA requirements. As a practical matter, however, the de novo process is complex, lengthy, and burdensome, largely because the submitter first must file a 510(k) and have it determined “not substantially equivalent” before it can proceed with the de novo process. CDRH’s report suggests presubmission discussions with review staff and establishment of a generic set of controls to serve as baseline special controls for devices classified through the de novo process. Legislation, however, may be needed to achieve meaningful streamlining of the process.

8. **Use of postmarket authorities:** Explore the greater use of postmarket authorities, including use of postmarket surveillance studies, as a condition of clearance for certain devices.

CDRH has no explicit authority to order postmarket surveillance studies as a condition of clearance. Because it is not always feasible to conduct large-scale clinical trials prior to clearance, the 510(k) Working Group recommends that CDRH explore seeking broader authority to require “condition of clearance” studies.

9. **GMP compliance as a prerequisite to clearance:** Clarify when it is appropriate to withhold clearance on the basis of failure to comply with good manufacturing requirements, and provide guidance on the use of preclearance inspections for class IIb devices.

The 510(k) Working Group notes that CDRH has statutory authority to withhold clearance for noncompliance with GMPs, when such noncompliance “will potentially present a serious risk to human health.” Although FDA has been reluctant to apply this authority to require preclearance inspections, the 510(k) Working Group found that preclearance inspections may be appropriate in some cases.

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

In the report, the 510(k) Working Group found that employee turnover has an adverse affect on the 510(k) review period because less experienced reviewers tend to create more withdrawals, more review cycles, and longer review documents. Reviewer experience and the ability of staff across CDRH to work together on cross-cutting issues were identified as critical factors for review quality and consistency.

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

1. **“Least burdensome” provisions:** Revise the 2002 “least burdensome” guidance to clarify the Center’s interpretation of the “least burdensome” provisions of the Federal Food, Drug, and Cosmetic Act.

CDRH staff expressed concern to the Task Force that industry’s understanding of the “least burdensome” provisions presented challenges during a 510(k) review and, in particular, CDRH’s attempts to obtain additional information to address a safety or effectiveness concern based on new scientific information when such information was not required for a predicate device. These types of requests, according to the report, often led to complaints of an “uneven playing field” that were raised with the CDRH ombudsman. The Task Force recommends that CDRH revise the “least burdensome” guidance to clarify that the provision is intended to eliminate unjustified burdens on industry, but not to “excuse industry from pertinent regulatory obligations nor to lower the agency’s expectations” regarding what is required to demonstrate that a device meets the relevant statutory standard. It is not clear, however, that such a clarification would eliminate objections to these types of information requests for 510(k)s, as CDRH’s review authority is limited to assessing the substantial equivalence of a device to the predicate device, and does not include the review of the safety or effectiveness of the device based on new scientific information. Nonetheless, the intent behind this recommendation could increase 510(k) data

burdens, and, thus, industry comments on this recommendation and participation in the development of any revised guidance will be critical.

2. **Quality of clinical data:** Improve the quality of the design and performance of clinical trials used to support PMA applications, in part by taking the following steps:
  - Develop guidance on the design of clinical trials that support PMA applications and establishing an internal team of clinical trial experts
  - Consider expanding ongoing clinical trial efforts to include clinical trials that support 510(k)s
  - Continue to engage in the development of domestic and international consensus standards to help establish basic guidelines for clinical trial design, performance, and reporting
  - Characterize the root causes of existing challenges and trends in Investigational Device Exemption (IDE) review and decision making
3. **Postmarket oversight:** Continue to develop better data sources, methods, and tools for collecting and analyzing meaningful postmarket information, including adverse event reporting.

The Task Force found that current postmarket surveillance efforts are hampered by the lack of information sources and the known limitations associated with medical device reports (MDRs), including reporting biases, varying reporting practices, underreporting, and the reporting of information insufficient to properly assess adverse events.

4. **Responding to new scientific information:** Establish and adhere to a predictable approach for determining what action, if any, is warranted for a product or group of products based on new scientific information.

Currently, CDRH staff respond to new scientific information on a case-by-case basis and there is wide variation on how such issues are handled. There is no clear or uniform policy on when postmarket safety or effectiveness issues justify a modification to premarket requirements. The Task Force proposed a new four-step framework for a process to determine how to respond to new information that may alter CDRH's understanding of the device's safety and effectiveness. The process comprises four key steps: detection, escalation, deliberation, and action.

The proposed framework would include establishing a Center Science Council, composed of experienced managers and employees and under the direction of the newly created Deputy Center Director for Science position.<sup>1</sup> Consistent with President Obama's memorandum on scientific integrity,<sup>2</sup> this standing body would be responsible for the following:

- Overseeing science-based decision making across the Center, including premarket review
- Periodically auditing decisions and assessing program performance
- Acting as a resource for staff on scientific questions, to support greater consistency in decision making and the treatment of cross-cutting issues

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<sup>1</sup> In conjunction with the CDRH Preliminary Reports, Dr. Jeffrey Shuren announced the appointment of a long-time FDA consultant, William Maisel, as CDRH's Deputy Center Director for Science and Chief Scientist beginning August 15, 2010.

<sup>2</sup> Obama, B., "Memorandum for the Heads of Executive Departments and Agencies" (March 9, 2009).

5. **Transparency:** Improve transparency and Web-based resources to provide meaningful and up-to-date information to all affected parties.

The Task Force reported concerns that CDRH often does not provide an adequate rationale when it makes changes in response to new science. To address these concerns, the Task Force recommends that CDRH develop a procedure for responding to new scientific information based on the framework discussed above and require that all actions taken on the basis of new information be promptly and clearly communicated to all affected parties. The report further recommends that CDRH release summaries of 510(k) reviews and other premarket review decisions not currently made public and release the results of postapproval and postmarket surveillance studies (to the extent permitted by law).

6. **Communication of changes:** Establish a standardized practice for “Notice to Industry” communications to more rapidly communicate changes in regulatory expectations.

The Task Force recommended CDRH use “Notice to Industry” letters to streamline the length of time it takes CDRH to develop guidance and communicate changes in regulatory expectations. The report recommends adopting a uniform template and terminology for “Notice to Industry” letters, including clear and consistent language to indicate that CDRH has changed its regulatory expectations, the general nature of the change, and the rationale for the change. “Notice to Industry” letters would likely be considered “Level 1 – Immediately in Effect” guidance documents, and would open a public docket in conjunction with their issuance through a notice of availability in the *Federal Register*. When appropriate, these letters would be followed up as soon as possible with new or modified guidance explaining CDRH’s new regulatory expectations in greater detail and revising the guidance where necessary in response to comments received.

7. **Internal staff and expertise:** Assess staffing needs for mission-critical functions and anticipated scientific challenges, and enhance employee training and professional development to ensure current staff can perform at an optimal level.

The Task Force noted that CDRH staff face difficulties identifying and accessing scientific experts in specific areas. Staffing is not optimal to meet anticipated demands, and there are too few experts within each content area to support CDRH’s needs.

8. **External experts:** Establish a network of external experts to better inform the review of cutting-edge technologies.

The report recognizes that it is unrealistic for CDRH to maintain “cutting-edge expertise and experience in-house,” particularly for novel technologies, and recommends that CDRH improve its mechanisms for leveraging external scientific expertise in a timely manner. The Task Force recommends that CDRH develop a Web-based network of external experts, using social media technology, in order to appropriately and efficiently leverage external expertise that can help CDRH staff better understand novel technologies, address scientific questions, and enhance CDRH’s scientific capabilities. Additionally, the Task Force recommends that CDRH assess ways in which CDRH staff members could engage with external experts informally as well as formally to improve and update their scientific knowledge.

9. **Review workload:** Consider creating a standardized mechanism for the rapid assembly of an ad hoc team of experienced review staff from multiple divisions to temporarily assist with time-critical work in a particular product area.

FDA will make decisions about adopting or rejecting the changes recommended by the 510(k) Working Group and the Task Force on the Utilization of Science in Regulatory Decision Making after evaluating public comments received in response to the two reports. CDRH's goal is to begin implementation of the noncontroversial, short-term changes recommended by the 510(k) Working Group following evaluation of the public comments in the fall of 2010.

If you have any questions about the issues described in this LawFlash, or would like assistance with preparation of comments to FDA on the recommendations, please contact either of the following Morgan Lewis attorneys:

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