For more information, contact:

Edward M. Basile
+1 (202) 626 2903
ebasile@kslaw.com

Laurie A. Clarke
+1 (202) 626 2645
lclarke@kslaw.com

Pamela Forrest
+1 (202) 661 7888
pforrest@kslaw.com

Beverly H. Lorell, MD
+1 (202) 383 8937
blorell@kslaw.com

Jessica Ringel
+1 (202) 626 9259
jringel@kslaw.com

Elaine H. Tseng
+1 (415) 318 1240
etseng@kslaw.com

Lynette Zentgraft
+1 (202) 626 2996
lzentgraft@kslaw.com

King & Spalding
Washington, D.C.
1700 Pennsylvania Avenue, NW
Washington, D.C. 20006-4707
Tel: +1 (202) 737 0500
Fax: +1 (202) 626 3737

San Francisco
101 Second Street
Suite 2300
San Francisco, CA 94105
Tel: +1 (415) 318 1200
Fax: +1 (415) 318 1300

www.kslaw.com

August 31, 2010

FDA Issues Preliminary Reports on Changes to the 510(k) Process and the Use of Science in Regulatory Decision-Making

On August 4, 2010, the U.S. Food & Drug Administration (FDA or the Agency) issued two preliminary reports that recommend changes in the 510(k) premarket notification process and procedures for the use of science in regulatory decision-making.[1] The reports, which were developed by two internal FDA committees, were based on comments FDA received in response to the Agency's four sets of questions about the 510(k) process published in the *Federal Register* on February 18, 2010, public meetings on these topics, analyses of internal data, and interviews of FDA staff.

The preliminary report of the 510(k) Working Group (the 510(k) Report) includes its findings regarding the 510(k) process and its recommendations to "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." The preliminary report of the Task Force on the Utilization of Science in Regulatory Decision Making (the Science Report) describes proposals for rapid incorporation of new scientific information in the review process, as well as strengthening the rigor of clinical investigations that support premarket submissions. The two reports, which cross reference each other, focus on changes that are feasible within the current statutory framework. FDA has requested written comments on the preliminary reports by October 4, 2010.[2] FDA stated that it might refer some proposed changes to the Institute of Medicine for further review.

This Client Alert summarizes the recommendations and the issues for consideration identified in those preliminary reports (collectively "recommendations") that we believe are likely to have the most impact on FDA's regulation of devices, if implemented, and analyzes their potential impact, if implemented. The attached table provides more detailed information and analysis for all the recommendations listed in the reports.

Key Recommendations in the 510(k) Report

The 510(k) Report focuses on three broad topics: (1) the need for a rational, well-defined, consistently interpreted review standard; (2) the need for well-informed decision making; and (3) the need to provide continuous quality assurance. We believe that the following are the key recommendations and issues for consideration identified in the report:

- **The consolidation of "indication for use" and "intended use."** The preliminary report recommends that: (1) FDA retain the term "intended use" and merge "indications for use" into it; and (2) define "intended use" so it is clear what characteristics it includes. The Working Group notes that confusion about the terms has led to inconsistency in reviewers' determination of whether a new device has the same "intended use" as a predicate device, which is required for a finding of substantial equivalence. The potential impact of this change is that minor wording differences could lead to denial of 510(k) clearance. The actual impact will depend in part on how FDA defines "intended use". The preliminary report does not include a proposed definition.
- **Express authority to consider off-label uses during 510(k) review.** The preliminary report suggests that FDA consider seeking expanded authority to consider off-label uses when determining a device's intended use. The report expressed concern that an off-label use might be a device's primary intended use, but FDA could clear the device without considering the efficacy and safety of that off-label use. The report indicates that FDA's issuance of a substantial equivalence with limitations letter, which requires the labeling for the device to disclose information about that off-label use, might not provide adequate protection. The potential impact is FDA could require companies to provide safety and effectiveness data for uses for which they do not intended the device to be used. Congress previously enacted the current statutory limitations on FDA's authority to consider off-label uses during the review of 510(k) notices to avoid that burden.
- **Concerns about predicate quality.** In the 510(k) report, the Working Group expresses concerns about predicates that are older, poorly-performing, recalled, or have several generations of predicates between it and the original device. The Working Group's only suggestion to address these concerns is that FDA consider developing "guidance on when a device should no longer be available for use as a predicate." Any such guidance could limit the pool of eligible predicates. If FDA were to require a comparison to the original device on which the substantial equivalence of its predicate device is based, the manufacturer would have to re-establish the safety and effectiveness of previously cleared indications and technological characteristics with each new device. This approach would likely hinder innovation.
- **Use of split predicates and multiple predicates.** The 510(k) Working Group recommended that FDA consider disallowing the use of split predicates, which they defined as a situation in which the manufacturer relies on one predicate for the device's "intended use" and another predicate for the device's technological characteristics. The Working Group also recommended issuing guidance regarding the "appropriate" use of multiple predicate devices. If FDA were to prohibit split predicates, the Agency would in essence limit predicate devices to those that are very similar to the new device with respect to intended use/indications and technological characteristics. If FDA were

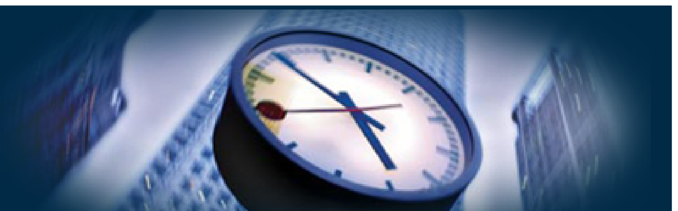
to also eliminate the distinction between intended use and indications for use, it likely would be harder for a potential predicate to meet the intended use requirement. If FDA limits the number of predicate devices, the manufacturer might have to choose between acceptable predicate devices. This restriction could prevent it from showing that some aspects of the device are not new because they are part of another legally marketed device. The combination of two or more of these recommended changes could make it exponentially more difficult to demonstrate substantial equivalence.

- **The creation of Class IIb Devices.** The Working Group recommended splitting current class II devices into two subsets, IIa and IIb. Class IIb devices would typically require submission of "clinical information, manufacturing information, or, potentially, additional evaluation in the postmarket setting" and develop associated guidance and training for reviewers and industry on this new classification subset. The classification of generic types of devices as Class IIb and the issuance of a guidance document identifying the minimum additional information required in 510(k) notices for Class IIb devices would help manufacturers of those generic types of devices provide the information needed to demonstrate substantial equivalence. However, it is unclear how FDA will handle 510(k) notices for modifications to a cleared Class IIb device because minor changes would not seem to require new clinical data, manufacturing information, and/or postmarket surveillance. The most likely scenario is that FDA and the manufacturer will analyze the modifications in the same manner as other 510(k) devices.

- **The rescission of device clearances.** The 510(k) Report states that FDA should issue "a regulation to define the scope, grounds, and appropriate procedures, including notice and an opportunity for a hearing, for the exercise of [FDA's] authority to fully or partially rescind a 510(k) clearance." The Working Group believes such a regulation is needed because it is unclear to both CDRH staff and industry under what circumstances FDA could and would rescind 510(k) clearance. The rescission of a 510(k) clearance could potentially call into question the clearances—and thus the continued availability—of any cleared device that used the device with a rescinded clearance as its predicate.

- **Streamlining the de novo review process for novel low risk devices**. The 510(k) Working Group recommended revising the guidance on de novo review of automatic Class III classification, clarifying FDA's evidentiary expectations, encouraging discussion between FDA and manufacturers to determine what information should be submitted rather than going through a full 510(k) review to determine eligibility for de novo classification, and establishing baseline special controls for "devices classified into class II through the de novo process and augmenting them with additional device-specific special controls as needed." Adoption of these recommendations would significantly improve review periods and predictability of the de novo review process.

- **Revising the device modifications guidance.** The 510(k) Working Group recommended that FDA revise the guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device" ("the Device Modifications Guidance") to clarify which modifications to 510(k) devices require a new traditional or abbreviated 510(k) notice, a Special 510(k) notice, or documentation in an internal memorandum-to-file. The Working Group further suggested that CDRH explore whether



it is feasible to require regular, periodic updates listing modifications to 510(k) devices with explanations of why a new 510(k) was not filed. The 510(k) Report cited concerns that manufacturers believe that new 510(k)s are only required when a modification definitively or negatively affects safety or effectiveness. Additionally, the report noted that manufacturers may make a series of minor changes that cumulatively affect safety and effectiveness. The report also noted that CDRH lacks necessary safety and effectiveness information when 510(k) notices are not filed for modifications. A revised Device Modifications Guidance would probably require 510(k) clearance for more types of device modifications. A periodic reporting requirement would mean the manufacturers would have to inform FDA of any modifications made in the past year and thus, the Agency would have the opportunity to review and possibly object to changes made without new 510(k) clearance. In that case, FDA could require new 510(k) clearance (or possibly PMA approval depending on the change) and the Agency might take enforcement action, such as issuing a warning letter.

- **Implementation of an assurance case framework.** The 510(k) Report suggests implementing an "assurance case" framework, which FDA defines as "a formal method for demonstrating the validity of a claim by providing a convincing argument together with supporting evidence", and develop guidance and training programs. The basis for this recommendation is that unclear or otherwise insufficient 510(k) submissions are difficult to review, increase review times and make it difficult to "efficiently identify the critical features of a new device and the relevant points of comparison to the predicate." Implementation of the proposed assurance case framework would probably require 510(k) notices to include more information and data to support changes, which in turn, would likely lead to delays and increased costs in obtaining clearance.

- **The summary of safety and effectiveness information.** The 510(k) Report suggests the Agency consider revising 21 C.F.R. § 807.87 to require a list and 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 Working Group suggests that the regulations do not state what clinical or scientific information may be necessary to support a 510(k) submission, and submissions frequently do not contain sufficient information, leading to delays in the review and clearance of submissions. A requirement to list and describe all scientific information regarding the safety and/or effectiveness of a new device that is known or that should be reasonably known to the submitter would require the manufacturer to conduct an extensive literature search and prepare a detailed summary and analysis of all published information about the safety or effectiveness of the device, even if it were not supportive, that is the subject of the 510(k) notice. In addition, manufacturers would have to describe any information they possess from testing, complaints, or that it acquired by other means. This requirement would significantly increase the cost and time to prepare a 510(k) notice. In addition, the manufacturer could be subject to criminal penalties if FDA concludes that the information it provided was incomplete or inaccurate. The 510(k) Report also fails to describe how the summary of safety and effectiveness information would be used in determining whether a device is substantially equivalent to its predicate(s).

- **Submission of photographs and schematics, and retention of a sample device.** In the interest of "efficiently identify[ing] the critical features of a new device and the relevant points of comparison to the predicate," the Working Group recommends that manufacturers be required to submit photographs and schematics with a 510(k) submission. Elsewhere in the 510(k) Report, the Working Group further recommends that any non-proprietary photographs and schematics be included in the publicly-available 510(k) database. Additionally, the Working Group recommends that manufacturers be required to keep at least one unit of a device on hand for CDRH's review either during the device's clearance or during future reviews when the device is listed as a predicate. This requirement would be burdensome for some manufacturers and would benefit competitors who use their device as a predicate.
- **Inclusion of manufacturing process information in 510(k) submission.** The Working Group suggests that CDRH use guidance to explain when it will require manufacturing process information to support a 510(k) submission and require pre-clearance inspections. The Working Group also suggests that FDA consider seeking authority to withhold clearance based on quality system regulation violations. One of the major differences between the PMA and 510(k) pathways is that PMA devices are subject to premarket manufacturing evaluations, whereas this evaluation occurs postmarket for 510(k) devices. These manufacturing requirements would significantly increase the cost and time to obtain clearance.
- **CDRH clearance of final device labeling and requirement of periodic labeling updates.** The Working Group recommends that CDHR "explore" whether to require clearance of final device labeling and whether to require manufacturers to submit periodic labeling updates. The 510(k) Report also suggests that the final cleared labeling and up-to-date labeling be posted on FDA's website. If FDA posted the devices' cleared labeling on the Agency's website it would be easy to identify the cleared claim, as well as changes to the labeling. The manufacturers would benefit from the certainty that FDA cleared the claims in the labeling. However, FDA could take enforcement action and competitors could request that FDA take enforcement action by identifying changes to the labeling for which new 510(k) clearance was required but not obtained.

Key Proposals of the Science Report

The Task Force focused on three areas related to FDA's use of new science and information in its regulatory decision-making for medical devices: enhancing CDRH's knowledge base, the ability to rapidly incorporate new science and modify decision-making by CDRH, and ensuring that actions to be taken are communicated broadly and as rapidly as possible. The Science Report provides multiple proposals to improve CDRH's scientific knowledge base, apply a predictable approach to determine the appropriate response to new science, and rapidly communicate the Center's current or evolving thinking to affected parties. The proposed recommendations that may have the greatest potential on the device industry are summarized below.

- **Improvement in quality of clinical data supporting premarket applications.** The Science Report aligns with the opinion in the 510(k) Report that "*Some innovations in device design raise questions of safety and effectiveness that can only be answered with clinical data.*" Both reports acknowledge

the need for more predictability about whether clinical data is needed and the type of clinical data that may be required to support clearance or approval of certain medical devices. The Science Report discusses the inconsistent quality of data and deficiencies in the design and conduct of clinical trials conducted under an Investigational Device Exemption (IDE) that are intended to support PMA approval or 510(k) clearance. Among several recommendations, it advises that FDA expand its processes to improve the clinical trials that support PMA approval to include clinical trials that support 510(k) clearance. Additionally, the Science Report recommends CDRH establish a team of clinical trial experts who would provide support to other CDRH staff regarding the design of specific clinical device trials. The team would serve as a review board when there are differences of opinion about appropriate clinical trial design and help assure proper and consistent application the least burdensome principles.

- **Use of external experts.** The Task Force provides several recommendations that are intended to improve CDRH's internal processes and staffing for data collection and interrogation, integration of internal expertise, and conduct of analyses applicable to premarket review and postmarket oversight. In addition, it recommends that CDRH develop a web-based network of external experts to help the staff understand novel technologies and address scientific questions, including those related to clinical care. This proposed process has the potential to enhance the technologic and clinical knowledge base of CDRH and it may be particularly applicable to the review of very novel devices. However, an enhanced reliance on external experts also carries the potential that the Center's decision-making may be profoundly influenced by external parties and the Science Report does not include recommendations for considering or communicating to the manufacturer or public the identities, opinions, or potential biases of the external expert.
- **Development of a four-step conceptual framework to respond to new scientific information: detection, escalation, collaborative deliberation, and action.**
  - **Detection and Escalation.** A major recommendation describes a proposal for Center-wide "Signal Escalation" process following the emergence of new scientific information that may alter CDRH's understanding of a device's safety or effectiveness. The proposal would enable the detection and rapid escalation of the new signal to higher levels of management. This proposal would build on processes that are already under development in CDRH to more rapidly respond to postmarket safety signals. The proposal lacks, however, detailed processes and definitions that would assure consistent implementation of the process.
  - **Collaborative Deliberation and Action.** The Task Force identified several issues that should be considered when deliberating the new information and what, if any, action should be taken based on the new information. Notably, the Task Force recommended the establishment of a Center Science Council that would include experienced employees and managers to help assure consistency across the Center in responding to new information. The Science Report also outlined the various actions, public and non-public, that the Agency could take in response to new information about a device or group of devices.

- **Rapid communication of changes in CDRH's thinking.** To ensure broad and fast communication of changes in CDRH's thinking due to new scientific information, the Task Force advises that the Center should make use of new rapid communication tools. The report suggests streamlining the processes for developing guidance documents, reviewing reclassification petitions, and other currently available tools, but recognizes that these processes are slow. Therefore, the Science Report sets forth several other options:
  - CDRH should establish as a standard practice the issuance of open "**Notice to Industry Letters**" to manufacturers of a particular group of devices for which the Center has changed its regulatory expectations. The Task Force observes that a "Notice to Industry" would likely be considered as "Level 1 - Immediately in Effect" guidance accompanied by opening of a public docket and notice in the Federal Register and followed by more detailed guidance.
  - The posting 510(k) decision summaries on the publicly available 510(k) database website; and
  - The posting of cleared and up-to-date labeling for 510(k) cleared devices.

Conclusion

The attached table summarizes all the recommended changes and analyzes their potential impacts. We urge you to carefully read the two FDA reports, as well as that table. We welcome your views on the recommendations contained in those reports before October 4, 2010 as we intend to submit comments to FDA about them by that deadline. In addition, we encourage you to consider submitting written comments about those recommendations. Please contact us if you have questions regarding FDA's reports or if we can assist you in preparing comments about them.

Celebrating 125 years of service, King & Spalding is an international law firm with more than 800 lawyers in Abu Dhabi, Atlanta, Austin, Charlotte, Dubai, Frankfurt, Geneva, Houston, London, New York, Paris, Riyadh (affiliated office), San Francisco, Silicon Valley and Washington, D.C. The firm represents half of the Fortune 100 and, according to a Corporate Counsel *survey in August 2009, ranks fifth in its total number of representations of those companies. For additional information, visit www.kslaw.com..*

This alert provides a general summary of recent legal developments. It is not intended to be and should not be relied upon as legal advice.

[1] Federal Register. 75:47307. August 5, 2010. Both reports and related FDA announcements are accessible at, http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm220272.htm

[2] Comments, identified by Docket No. FDA-2010-N-0348, may be submitted electronically to http://www.regulations.gov. Written comments may be submitted to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.