FDA Issues Final Guidance on Evaluating Substantial Equivalence in 510(k) Submissions

On July 28, 2014, the Food and Drug Administration ("FDA") issued final guidance regarding the agency's substantive review of Traditional 510(k) premarket notifications. This document, titled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications," marks a key milestone in FDA's re-evaluation of the 510(k) program, which the agency initiated in 2009 in response to concerns that the program did not sufficiently assure the safety and effectiveness of devices as well as industry concerns that the program had become unpredictable and opaque.

Below we summarize the key points from the guidance, discuss how FDA responded to criticisms of the draft version of this guidance, and describe further actions that remain to be completed as part of FDA's 510(k) re-evaluation project.

Key Points from the Guidance

The new guidance is FDA's first update to the 1986 "blue book" document, "Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3." FDA asserts that it developed the guidance to inform industry and FDA staff about the agency's "current review practices," not to "implement significant policy changes." Key points from the guidance include.

Elimination of split predicates. The guidance states that the use of a "split predicate" is inconsistent with the 510(k) regulatory standard for demonstrating substantial equivalence. A 510(k) uses a "split predicate" when it compares the device that is the subject of the 510(k) (the "new device") against one predicate device to show sameness of intended use, and a separate predicate device with a different intended use to show similarity of technological characteristics. Although FDA has been taking this position in practice for several years, this is the agency's first official, final policy statement on this topic.

Designation of a "primary predicate." Unlike split predicates, FDA will accept multiple predicates in some circumstances. Multiple predicates are commonly relied upon when a 510(k) combines features from two or more previously marketed devices into a single, new device. In the guidance, FDA generally encourages the use of a single predicate to simplify the decision-making process. It also recommends that, when a manufacturer relies upon multiple predicates, the 510(k) identifies the "primary predicate," which is "the one with indications for use and technological characteristics most similar" to the new device.

Explanation of "reference devices." The guidance discusses the use of "reference devices," which, like the term "primary predicate," does not appear in the statute or FDA regulations. Reference devices are legally marketed devices, other than the predicate device(s), that are referred to in a 510(k) to help support the use of particular scientific methods or reference values. The guidance states that a manufacturer intending to rely upon a reference device should provide a scientific rationale for its use.

Definitions of "intended use" and "indications for use." FDA has long recognized a distinction between the "intended use" of a new device, which must be the *same* as the intended use of the predicate device, and the "indications for use" of a device, which may differ to some extent between the new and predicate device. In the guidance, FDA defines "intended use" to mean the "general purpose of the device or its function," whereas "indications for use" means "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." FDA also repeats the point it has made elsewhere that a manufacturer's intended use for a device can, in some cases, be determined by facts and circumstances outside the 510(k) submission itself. Although these concepts may

sound straightforward, identification of the "intended use" of a device can be a matter of negotiation, and in some cases dispute, between manufacturers and FDA.

Determining whether new "indications for use" constitute a different "intended use." According to the guidance, FDA may find that changes in indications for use constitute a different intended use when they raise a safety or effectiveness issue not raised by the predicate or have the potential to significantly increase a safety or effectiveness concern raised by the predicate. The guidance contains several illustrative examples of how FDA applies this concept. It also asserts that FDA may rely upon publicly available scientific information or FDA knowledge about how a disease progresses to determine whether indications to treat a certain disease or anatomical site constitute a new intended use.

Determining whether differences in technological characteristics raise different questions of safety and effectiveness. Where differences in the technological characteristics of a new device raise different questions of safety and effectiveness, the new device is not substantially equivalent to the predicate. The guidance describes a logic scheme by which FDA identifies the technological characteristics of a device, compares them against those of the predicate device, and then determines whether there are differences in technological characteristics that raise different questions of safety and effectiveness. FDA states that a "different question of safety and effectiveness" is a question "raised by the technological characteristics of the new device that was not applicable to the predicate device, and poses a significant safety or effectiveness concern for the new device." Similar to the section of the guidance addressing indications for use, this section of the guidance relies largely on illustrative examples.

Performance data requirements. If the new device described in a 510(k) has the same intended use as the predicate and the differences in technological characteristics do not raise new questions of safety and effectiveness, the remaining statutory question is whether the 510(k) contains information deemed necessary by FDA to demonstrate that the new device is "as safe and effective" as the predicate. The guidance does not discuss this statutory standard at this point in the logic scheme, most likely because FDA's interpretation and application of that standard is discussed in a separate draft guidance issued on July 15, 2014, titled "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics." Instead, the guidance discusses how FDA applies the statutory "least burdensome" principles by applying a hierarchy of performance data requests starting with descriptive information only, and then proceeding stepwise to include non-clinical bench testing and biocompatibility data, analytical studies using clinical samples (e.g., for in vitro diagnostic devices), and clinical performance data if required.

Encouraging 510(k) "Summaries" rather than 510(k) "Statements." FDA regulations require a 510(k) submission to include either a "510(k) Summary" or a "510(k) Statement." A 510(k) Statement is a certification that the manufacturer will make available all safety and effectiveness information in a cleared 510(k) within 30 days of request by any person, other than permitted redactions for patient privacy and trade secret protection. Because FDA can and does proactively post 510(k) Summaries on its website, which facilitates transparency, the guidance "encourages all submitters to utilize the 510(k) Summary option."

Encouraging greater transparency in 510(k) Summaries. The guidance states that FDA, in an effort to improve the transparency and predictability of the 510(k) program, intends to verify the completeness of the information a manufacturer submits in a 510(k) Summary. The guidance includes appendices describing the content required to be included in such summaries under FDA regulations, provides guidance on what information and data should be included, and includes a sample 510(k) Summary. In particular, the level of detail FDA is requesting be included with respect to clinical studies may be greater than manufacturers have been accustomed to providing in the past.

Responses to Criticisms of the Draft Guidance

On December 27, 2011, FDA announced the availability of a draft version of the 510(k) guidance and invited public comment. FDA received numerous comments, but ultimately made few significant changes to the guidance document. The principal changes were to:

- Expand the discussion of the use of predicate devices and the reasons for defining a "primary predicate";
- Add examples to several sections to clarify FDA's decision-making process for finding devices substantially equivalent despite differences in indications for use, technological characteristics, or performance characteristics;
- Add an appendix with a sample 510(k) Summary to demonstrate that level of detail FDA expects; and
- Remove sections of the draft addressing Special 510(k)s and Abbreviated 510(k)s, due to the relationship between Special 510(k)s and planned FDA guidance on submitting a new 510(k) for a device modification.

What's Next?

It appears that criticism of the 510(k) program has abated somewhat since FDA launched its re-evaluation initiative in 2009. Nevertheless, there are concerns that the 510(k) guidance reflects narrowed interpretations of the substantial equivalence standard that should have been subject to notice and comment rulemaking under the Administrative Procedure Act. Whether FDA's 510(k) policies or individual 510(k) decisions will be subject to more frequent appeals within FDA, or legal challenges in court, remains to be seen.

Although it has now finalized the 510(k) guidance, FDA has yet to complete a number of other important actions relating to the 510(k) program. These include:

- Issuing new draft guidance on when modifications to a device are significant enough to require a new 510(k), after having been required by Congress to withdraw its previous draft guidance from August 2011 on this subject;
- Issuing new guidance on Special and Abbreviated 510(k)s; and
- Considering comments received in response to the recent draft guidance, "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics."

In addition, FDA in the past has stated that it intends to develop new regulations relating to the transfer of ownership of 510(k)s and to develop a public repository of medical device labeling. Ropes & Gray will continue to monitor developments on these proposed initiatives, and other aspects of the 510(k) program.

For more information, please contact any member of Ropes & Gray's FDA regulatory practice or your usual Ropes & Gray Advisor.