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

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On July 28, 2014, the U.S. Food and Drug Administration (FDA) released a final guidance entitled, "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance for Industry and Food and Drug Administration Staff". [hereinafter "Final Guidance"][1] The Final Guidance provides industry and FDA staff with explanations about the critical decision points that FDA uses to determine substantial equivalence and is intended to enhance the predictability, consistency, and transparency of the 510(k) program. A draft version of this guidance was published two and a half years ago in December 2011.

In large measure, the Final Guidance carries forward the principal features of the 2011 draft and, indeed, FDA acknowledges that the guidance is "not intended to implement significant policy changes to the current 510(k) review process."[2] However, the agency noted that sections addressing FDA's Special and Abbreviated 510(k) programs, which were included in the 2011 draft, would be finalized by the agency separately.[3] We will not discuss those programs here.

The Final Guidance incorporates four appendices that are particularly useful:

- (A) 510(k) Decision-Making Flowchart (which is modified from the draft guidance);
- (B) the 510(k) Summary Document Requirements;
- (C) Sample of 510(k) Summary Complying with 21 C.F.R. § 807.92, and
- (D) a Glossary of Significant Terminology.

Additionally, the principles in the Final Guidance should be supplemented by a careful review of a new draft guidance, issued by FDA on July 14, 2014, (not discussed here) outlining the benefit-risk factors FDA considers to determine whether a 510(k) device with different technological characteristics is substantially equivalent.[4]

Overview

The Final Guidance provides updated information to the existing guidance document entitled "Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3 (hereinafter "K86-3 Guidance"), issued on June 30, 1986. The K86-3 Guidance was written and issued as final guidance prior to the February 27, 1997 implementation of FDA's Good Guidance Practices and has not been updated since its initial publication date. This Final Guidance replaces the K86-3 Guidance.

The Final Guidance, thus, represents FDA's current recommendations to industry and agency staff about the content of 510(k) premarket notification submissions and describes the decision-making process for determining substantial equivalence of devices reviewed under the 510(k) program.

1 The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance for Industry and Food and Drug Administration Staff, available at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm284443.pdf.

2 Id. at 1.

3 Until FDA issues new final recommendations for Special and Abbreviated 510(k)s, the recommendations in "The New 510(k) Paradigm-Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications, " dated March 20, 1998, remain in effect.

4 Available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm282958.htm.

The Final Guidance is organized to coincide with the critical decision points outlined in the 510(k) Decision-Making Flowchart, which itself has been updated to track Section 513(i) of the Federal Food, Drug, and Cosmetic Act (FDCA)[5] and relevant regulations more closely. The Final Guidance is not intended to supplant existing device-specific guidance, and FDA notes that the Final Guidance covers broader areas not addressed in the device-specific guidance documents. Also, FDA states that the 510(k) Decision-Making Flowchart is meant to be used only in conjunction with this Final Guidance and not as a "stand-alone" document. In short, the relevant parts of the Final Guidance should be consulted in the context of each critical decision point in the Flowchart.

Major Points

The Final Guidance provides useful commentary on the entirety of the 510(k) program. FDA's recommendations on the following major points are especially noteworthy:

1. **The appropriate use of multiple predicates and the prohibition of the use of split predicates**

The review standard for 510(k) submissions is substantial equivalence of the new device to a legally marketed device. Under 21 C.F.R. § 807.92(a)(3), a "legally marketed device" is a device that (i) was legally marketed prior to May 28, 1976 (a preamendment device) and for which a premarket approval application is not required; **or** (ii) has been reclassified from Class III to Class II or I; **or** (iii) has been found substantially equivalent through the 510(k) process. For purposes of determining substantial equivalence, the legally marketed device is commonly referred to as the "predicate device" or "predicate." While manufacturers may identify more than one predicate device, only one is required. The Final Guidance calls attention to FDA's preference that manufacturers identify a single predicate device when possible to simplify and facilitate decision-making, but confirms that multiple predicates may be identified. When multiple predicates are used, FDA recommends that a primary predicate be identified, which should be the one with indications for use and technological characteristics that are most similar to the device under review.

Of particular interest, is FDA's announcement that the use of a "split predicate" is inconsistent with the 510(k) regulatory standard. A "split predicate" refers to a situation in which a manufacturer is attempting to "split" the 510(k) decision-making process by demonstrating that a new device has the same intended use as one marketed device while comparing the new device's technological characteristics with a second marketed device that has a different intended use. Although the use of the split predicate method had previously been accepted by FDA, the agency now concludes that the use of split predicates is inconsistent with Section 513(i) of the FDCA and 21 C.F.R. § 807.100(b), which provide that, for a new device to be considered substantially equivalent to a predicate device, the new device must have the same intended use as the predicate and the same technological characteristics or different technological characteristics that do not raise different questions of safety and effectiveness than the predicate device.

Despite this change in direction regarding split predicates, FDA will continue to allow the use of multiple predicates. For example, the agency notes that multiple predicate devices are appropriate to help demonstrate substantial equivalence in several situations: (1) when combining features from two or more predicate devices with the same intended use into a single new device; (2) when seeking to market a device with more than one intended use; or (3) when seeking more than one indication for use under the same intended use.

The Final Guidance articulates several examples of how multiple predicates can be used to support substantial equivalence of a new device when combining the technological features of two or more predicates that have the same intended use, or when seeking more than one indication for use under the same broad intended use. In this regard, the Final Guidance reminds the reader that the term "intended use" means the general purpose of the device or its function, and encompasses the indications for use. The term "indications for use," on the other hand, as described in 21 C.F.R. § 814.20(b)(3)(i), characterizes the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

The Final Guidance also addresses the concept of a "reference device" which was first raised in the 2011 draft guidance.

5 21 U.S.C. § 360c(i).

A reference device is not a predicate device and it cannot be used to address Decision Points 1-4 on the Flowchart. FDA explains that it will rely on a "reference device" only in assessing the acceptability of the scientific methods or standard reference values at Decision Point 5a on the Flowchart. The Final Guidance provides two examples to illustrate the use of reference devices in situations where there are differences in the technology between the new device and the predicate device(s) and the FDA must determine whether the proposed scientific methods for evaluating the new/different characteristics' effects on safety and effectiveness are acceptable.

2. The processes associated with determining whether a new device with new indications for use has a new intended use

The Final Guidance notes that not every change in indications for use, which may affect safety or effectiveness, will result in a finding of a new intended use. Only a change in the indications for use that raises different questions of safety and effectiveness and, therefore, precludes a meaningful comparison with a predicate device constitutes a new intended use. FDA explains that the agency may find changes in indications for use of a device to constitute a new intended use when the changes raise a safety or effectiveness issue that was not raised by the predicate device, or where the changes have a significant potential to increase a safety or effectiveness concern by the predicate device. In the first case, reliance on a predicate device is inadequate because the safety or effectiveness issue was not considered in reviewing the 510(k) for the predicate device. In the second case, although the safety and effectiveness issue may have been considered, the finding of substantial equivalence for the predicate device cannot be generalized to the new indications for use because of a probable, significant change in the incidence or severity of the issue. In both cases, the predicate device is not an adequate proxy for an independent determination of safety and effectiveness.

3. The process for determining whether different technological characteristics raise different questions of safety and effectiveness

After FDA has determined that a valid predicate device exists for a new device and that both devices have the same intended use, FDA will compare the technological characteristics of the new device and the predicate device. The Final Guidance acknowledges that devices reviewed under the 510(k) program commonly have different technological characteristics from the predicate device(s). The Final Guidance recommends that to facilitate FDA's review of the new device's technological characteristics, the device description in the 510(k) should explain in sufficient detail the similarities in materials, design, energy source, and other device features between the new device and the predicate device(s). Examples of key characteristics that should be included are:

- An overall description of the device design, which may be facilitated by the submission of engineering drawings or other figures, including a diagram identifying how the different components of the device work together. The device description should also include a discussion of the physical specifications, dimensions, and design tolerance that are critical to the new device.
- A complete description of the materials used in the device. A complete identification of the chemical formulation used in the materials of construction, especially those that come into contact with the patient, should be provided.
- A description of energy sources, including not only energy delivery to the device, but also the energy delivery that is part of the functional aspect of the device and that affects the patient and/or the health care professional using the device.
- Other key technology features, such as software/hardware features, density, porosity, degradation characteristics, nature of reagents (*e.g.*, recombinant, plasma derived) and principle of the assay method should be included.

FDA recommends that once the technology characteristics of the new and predicate device(s) have been clearly identified, an assessment of the similarities/differences in technology should be identified, preferably in tabular format.

Finally, the Final Guidance provides several useful examples to illustrate how FDA will decide whether any differences in the technological characteristics raise different questions of safety and effectiveness for the new device as compared to the predicate device(s).[6]

6 Supra, note 1 at 21-22.

4. **When performance data, with special emphasis on clinical performance data, may be required**

The Final Guidance states that the type and quantity of performance data necessary to support a determination of substantial equivalence depend upon the device, the device type, or both, and notes that manufacturers should pay special attention to whether there are device-specific guidance or special controls for the device. When the descriptive information about materials, design, specifications, and other technological characteristics are not sufficient to support a substantial equivalence determination, FDA will likely request clinical performance data when non-clinical bench performance testing or non-clinical animal and/or biocompatibility studies are insufficient, or available scientific methods are not acceptable.

The Final Guidance lists examples of instances in which such performance data would be required. These include scenarios in which new or modified indications for use fall within the same intended use as a predicate device, or where the technological differences between the new device and predicate device are significant but do not support an immediate "not substantially equivalent" (NSE) decision.

5. **Development of the 510(k) Summary to promote greater transparency in the 510(k) decision-making process**

Appendix B of the Final Guidance describes the requirements of the content to be included in a 510(k) Summary and provides guidance on the information to be included to ensure (i) compliance with 21 C.F.R. § 807.92 and (2) consistency in the level of information conveyed and captured in 510(k) Summaries that are available to the public on FDA's website. In Appendix C, FDA provides a hypothetical 510(k) Summary to demonstrate the recommended level of detail for each section.

AGG Observations

- The Final Guidance's discussion of the 510(k) review process affirms that in most instances, FDA will issue a request for additional information or testing (rather than issuing a NSE decision letter) to allow manufacturers an opportunity to address the agency's concerns regarding the equivalency of a new device's intended use of technology. Moreover, the Final Guidance signals that the FDA will work with the manufacturer to attempt to resolve any perceived deficiencies in the submission.

- Manufacturers should give careful thought to the use of multiple predicates. Although the Final Guidance does not prohibit their use, it emphasizes the agency's preference for manufacturers to identify a single predicate device with indications for use and technological characteristics similar to that of the new device.

- FDA's decision that the "split predicate" method is inconsistent with the 510(k) regulatory standard has both positive and negative aspects. The use of split predicates has always increased the potential for derailment of a 510(k) determination of substantial equivalency and may be responsible, in part, with the industry's complaints about inconsistency and lack of transparency in FDA's decision-making process. Premarket notifications with split predicates also undoubtedly led to longer and less predictable review cycles. The now announced prohibition of split predicates may allow clearer and more effective decisions in the future. On the other hand, the change in approach will likely make it more difficult for manufacturers with breakthrough technologies to rely on the traditional 510(k) submission process and may also have a greater impact on start-up companies that have less experience navigating the 510(k) program requirements and selecting appropriate predicate device(s).

- The Final Guidance clarifies that, when FDA has determined that a new device has different technological characteristics from the predicate device, but those differences alone do not raise new questions of safety or effectiveness, the agency must evaluate the acceptability of the proposed scientific methods for evaluating the effects of the new or different technological features on the overall safety and effectiveness of the new device when compared to the predicate. To aid in this evaluation, the Final Guidance explains that a manufacturer may

benefit from using a "reference device" to direct the FDA's attention to similar situations that it has addressed previously in the 510(k) program. Although reference devices are not predicate devices, they may appropriately be used to support the acceptability of the scientific methodology or the standard reference values proposed by the manufacturer to establish the substantial equivalence of new technological characteristics of the new device that do not represent different questions of safety or effectiveness when compared to the predicate. The reference device concept is a new approach and the Final Guidance provides several examples to illustrate how the concept may be used. The examples show that if a manufacturer intends to use a reference device, the manufacturer must provide a scientific rationale to justify its use and also illustrate that when a selected reference device is used in an anatomical location or for a physiological purpose which is considerably different than that of the new device, its utility as a reference device will be limited.

- No 510(k) submission should be drafted without careful attention to the four appendices to the Final Guidance. As noted previously, the 510(k) Decision-making Flowchart, although a concept that has been used for some time, should not be used as a "stand-alone" document. The decision tree approach of the Flowchart must be supplemented by the narrative provided in the Final Guidance itself.

- Manufacturers, when preparing a 510(k) submission, should factor into the equation, the FDA's July draft guidance on benefit-risk factors in 510(k) submissions.[7] The stated purpose of that draft guidance is to assist FDA reviewers in making substantial equivalence determinations at the point when the agency has determined that a new device has different technological characteristics from the predicate device(s), but those differences do not raise new questions of safety or effectiveness. Because devices reviewed under the 510(k) program frequently have different technological characteristics from their predicate device(s), the collective wisdom in the Final Guidance and this draft guidance provide both new and valuable insights into FDA's decision-making process for substantial equivalency determinations.

- Finally, although the Final Guidance only represents FDA's current thinking on this topic, does not create or confer any rights for on any person, and does not operate to bind FDA or the public, a manufacturer who disregards its principles when preparing 510(k) submissions should not expect a favorable result.

Learn More about the Guidance

Join AGG's Food and Drug Practice leader, Alan Minsk for a one-hour complimentary webinar on September 16 from 12:00 pm – 1:00 pm EDT as he discusses what medical device manufacturers need to understand about the 510(k) guidance changes. This event is CLE approved. Please click here[8] to register.

7 Supra, Note 4.

8 https://event.on24.com/eventRegistration/EventLobbyServlet?target=reg20.jsp&eventid=835170&sessionid=1&key=7BF1DCB053F0E46B8788D6FBAEEAAB0F&sourcepage=register

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