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Client Alert

FDA & Life Sciences Practice Group

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FDA's Substantial Equivalence Guidance

Describes FDA's Process for Evaluating Substantial Equivalence and Updates to the 510(k) Decision Flowchart

The U.S. Food and Drug Administration (FDA) has issued a final guidance document titled *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (July 28, 2014)* ("SE Guidance").[1] The SE Guidance discusses FDA's process for evaluating 510(k) submissions and determining whether a new device is substantially equivalent (SE) to its predicate device(s). More specifically, the SE Guidance attempts to provide clarity on the following:

- Appropriate use of predicate devices, including multiple predicates;
- When new indications for use may be considered a new intended use;
- When different technological characteristics raise different questions of safety and effectiveness;
- When performance data, particularly clinical data, may be necessary to support an SE determination; and
- Preparation of 510(k) Summaries

The SE Guidance is applicable to 510(k) submissions reviewed by the Center for Devices and Radiological Health (CDRH), including the Office of Device Evaluation (ODE) and the Office of In Vitro Diagnostics and Radiological Health (OIR), and the Center for Biologics Evaluation and Research (CBER). The SE Guidance does not address Special or Abbreviated 510(k) submissions as FDA intends to address these in separate guidance. The SE Guidance also does not address issues specific to combination products.

Significantly, the SE Guidance replaces FDA's *Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum K86-3 (June 30, 1986)* ("K86-3 Memo") and revises the agency's long-standing 510(k) Decision Flowchart.

The SE Guidance provides several examples to illustrate how FDA will apply the 510(k) Decision Flowchart and other concepts outlined in the guidance in making substantial equivalence determinations. We have included some of

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the examples in this document; however, we strongly encourage you to read the SE Guidance in its entirety.

510(k) Decision Flowchart

In the SE Guidance, FDA states that the 510(k) Decision Flowchart was revised to more closely align with certain sections of the Federal Food, Drug, and Cosmetic Act (FDCA) and relevant regulations. The new 510(k) Decision Flowchart includes the following major decision points:

Decision 1: **Is the predicate device legally marketed?**

Decision 2: **Do the devices have the same intended use?**

Decision 3: **Do the device have the same technological characteristics?**

Decision 4: **Do the different technological characteristics of the device raise different questions of safety and effectiveness?**

Decision 5a: **Are the [scientific] methods acceptable?**

Decision 5b: **Do the data demonstrate substantial equivalence?**

FDA emphasizes the need to use the updated 510(k) Decision Flowchart in conjunction with the text of the SE Guidance. A copy of the new 510(k) Decision Flowchart is attached for reference.

Statutory Criteria for Substantial Equivalence

Section 513(f) of the FDCA states that a new[2] device is automatically in Class III unless the device is within a type of device introduced after May 28, 1976, that has been reclassified into Class I or II and is SE to another device within such classification.[3] The SE Guidance discusses the statutory standard for a finding of substantial equivalence and emphasizes that the 510(k) review process is both an assessment of the safety and effectiveness of a device and a means of classifying a device. If FDA determines that the device, as described in a 510(k) submission does not meet the criteria for a finding of substantial equivalence, FDA will issue a not substantially equivalent (NSE) order. The SE Guidance re-affirms "FDA's longstanding policy [of] treat[ing] NSE determinations as falling into two categories: (1) those that reflect FDA's affirmative determination that the device is a Class III device and cannot be reviewed in a 510(k) submission, and (2) those that reflect inadequacies in the evidence submitted that preclude a finding of substantial equivalence." The SE Guidance explains that in the event of the former, PMA approval will be needed, whereas for the latter type of NSE letter an applicant may resubmit a 510(k) for the device.

Predicate Devices

The SE Guidance clarifies the difference between multiple predicates and "split predicates," discusses the appropriate use of multiple predicate devices in a 510(k) submission, and describes the use of reference devices.

Multiple Predicates

According to the SE Guidance, comparison to a single predicate in a 510(k) submission is optimal; however, use of multiple predicates may be appropriate when "combining features from two or more predicate devices with the same intended use into a single new device, when seeking to market a device with more than one intended use, or when seeking more than one indication for use under the same intended use."[4]

If an applicant cites to multiple predicate devices FDA recommends identifying a "primary predicate" in the submission. The SE Guidance defines the primary predicate as the device "with indications for use and technological characteristics most similar to the device under review."[5] Identifying a primary predicate will help facilitate the 510(k) review

Split Predicates

The SE Guidance clearly states that use of "a 'split predicate' is inconsistent with the 510(k) regulatory standard"[6] and therefore cannot be used to support a substantial equivalence determination. A "split predicate" is defined as " 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."[7] As a general matter, FDA must be able to determine whether (1) a new device has the same intended use and (2) any different technological characteristics of the new device raise new questions of safety or effectiveness, using a single predicate device.

Reference Devices

Consistent with the draft version of the guidance, the final SE Guidance discusses the use of "reference devices." Reference devices may be used to make FDA aware of a device(s) that may incorporate similar technology but has a different intended use, to support the use of scientific methods, or to support cited standard reference values. The SE Guidance explicitly states that reference devices are not considered predicate devices and therefore cannot be used as a comparison of the intended use of a device or for evaluating whether differences in technological characteristics raise new questions of safety or effectiveness. FDA intends to review the applicability of a reference device on a case-by-case basis. FDA also recommends that "if a manufacturer intends to use a reference device, the manufacturer should provide a scientific rationale that justifies its use." [8]

When Different Indications for Use May Be Considered a New Intended Use

An area of concern for both FDA and industry is when new or different indications for use for a device result in a new intended use. The discussions in the final SE Guidance around the distinction between intended use and indications for use are consistent with FDA's historical interpretations of these terms as outlined in the superseded K86-3 Memo.

The Guidance emphasizes that differences between the indications for use of a new device and predicate must be analyzed carefully. FDA provides the following examples of indications for use that generally will be considered to constitute a new intended use "because they are more likely to significantly affect safety or effectiveness":

- a change from a functional/performance indication to a treatment or aesthetic indication;
- a change from a diagnostic indication to a screening indication, or vice versa;
- a change in the anatomical structure of use;
- a change in the patient population (e.g., adult versus pediatric; different disease populations);
- a change in the clinical context or setting (e.g., periodic monitoring versus continuous monitoring; hospital versus home use).[9]

When Different Technological Characteristics Raise Different Questions of Safety and Effectiveness

FDA regulations define technological characteristics to include the materials, design, energy source, and other features of a device.[10] In its SE Guidance, FDA instructs applicants to include all information necessary to explain the new and predicate devices'[11] and strongly encourages presenting a comparison of the technological characteristics between the

new device and predicate in table format. The guidance further explains that if "FDA determines that there are differences in the technological characteristics of the new device and the predicate device, FDA will review and evaluate all relevant information bearing on any such differences in technological characteristics to determine whether they raise different questions of safety and effectiveness for the new device as compared to the predicate device." "A 'different question of safety or 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." [12] The SE Guidance includes the following example:

> **Predicate:** A mechanical device used for embryo dissection
>
> **New Device:** An electrical device used for embryo dissection
>
> **Intended Use:** Same
>
> **Different questions of safety and effectiveness?** Yes
>
> **Why:** In this example, changing the process from a mechanical process to an electrical energy source (e.g., laser) changes the way the device operates and raises different safety concerns regarding how the heating aspect of the electrical mechanism affects the embryo. Because these types of questions were not necessary to take into account for the predicate device, the new device would be found NSE.[13]

The illustrative examples provided in the guidance suggest that FDA will not consider performance data (including clinical data) when evaluating whether technological differences between a new device and its predicate raise new questions of safety or effectiveness. In other words, performance data cannot be used to demonstrate that the different technological characteristics of a device do not raise new questions of safety or effectiveness. If applied stringently, this concept could increase the number of NSE decisions.

Requests for Performance Data

FDA acknowledges that descriptive data alone will likely not be sufficient to support most 510(k) submissions and therefore performance data should be included to support a substantial equivalence decision. The SE Guidance indicates that performance data should also be submitted to support claims or other statements about a new device included in the 510(k) or labeling. The Guidance explains FDA's intent to apply a stepwise analytical approach in requesting performance data and determining the type of performance data needed to support a finding of substantial equivalence. The SE Guidance indicates non-clinical animal and/or biocompatibility studies [will] typically be requested when other forms of non-clinical bench performance testing are not sufficient to demonstrate substantial equivalence.

In its Guidance, FDA explains that when non-clinical performance data are not sufficient or when valid scientific methods of analysis do not exist, FDA may request clinical performance data to support a substantial equivalence determination. FDA may also request clinical data for a 510(k) when the "technological differences between the new device and predicate device are significant but do not support an immediate NSE determination due to different questions of safety and effectiveness"[14] in order to evaluate the safety and effectiveness of the new device as compared to the predicate device. The SE Guidance outlines various common situations in which clinical data may be requested, including the following two scenarios:

> The manufacturer modifies the indications for use, explicitly or implicitly, by proposing a different surgical implantation method which also affects the indications for use, e.g., a minimally invasive procedure in place of an open procedure, and the safety and effectiveness of the new device cannot be adequately replicated or otherwise characterized in a non-clinical performance (including animal) test environment to adequately support

substantial equivalence to the predicate. Although on its face a minimally invasive procedure would appear to involve less serious risks than an open procedure, the minimally invasive procedure may be less effective or may present different but still serious risks.[15]

Some devices that display data about the patient's anatomy or physiology, e.g., glucose meters, pulse oximeters, blood pressure cuffs, are supported by software. If there is a change in the software that relates to how the software analyzes the patient's anatomy or physiology, the device may need to be tested on actual patients to assure that the software performs in a manner that is equivalent to the previous version. In this case, non-clinical data may not suffice.[16]

Preparation of 510(k) Summaries

In an effort to improve the transparency of substantial equivalence decisions, FDA intends to comprehensively review 510(k) Summaries included in 510(k) applications. The review will ensure the 510(k) Summary accurately reflects the information provided in a 510(k) submission upon which the substantial equivalence decision was made. This is consistent with our recent experience with 510(k) reviews and requests for modifications to 510(k) Summaries.

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King & Spalding will continue to follow updates to FDA's 510(k) program. Please contact us if you would like to discuss any aspects of this guidance.

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[1] FDA's SE Guidance is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf

[2] For this document a "new device" is either a completely new device or a modified version of a legally marketed device that would require a new 510(k).

[3] Section 513(f) of the FDCA states:

> (1) Any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, is classified in class III unless—
> (A) the device—
> (i) is within a type of device (I) which was introduced or delivered for introduction into interstate commerce for commercial distribution before such date and which is to be classified pursuant to subsection (b) of this section, or (II) which was not so introduced or delivered before such date and has been classified in class I or II, and
> (ii) is substantially equivalent to another device within such type, or
> (B) the Secretary in response to a petition submitted under paragraph (3) has classified such device in class I or II.

[4] SE Guidance at 11.

[5] *Id.*

[6] *Id.*

[7] *Id.*

[8] *Id.* at 13.

[9] *Id.* at 18.

[10] FDCA sec. 513(i)(1)(B) and 21 C.F.R § 807.100(b)(2)(ii)(A).
[11] SE Guidance at 17 and 20.
[12] *Id.* at 20.
[13] *Id.* at 21.
[14] *Id.* at 24.
[15] *Id.*
[16] *Id.* at 25.