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Client Alert

FDA & Life Sciences Practice Group

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FDA Issues Updated Draft Guidance on Device Modifications
More 510(k)s Submissions Expected

On July 27, 2011, the U.S. Food and Drug Administration (FDA or "the Agency") issued the much anticipated draft guidance addressing when modifications to cleared devices require new 510(k) premarket notifications. This new draft guidance, "510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device," when finalized, would supersede the Agency's 1997 guidance, "Deciding When to Submit a 510(k) for a Change in an Existing Device." Overall, the updated guidance will likely result in the filing of new 510(k)s and increase the total number of 510(k)s that manufacturers need to file. We recommend that all device manufacturers review their procedures for assessing modifications to their 510(k)-cleared devices, revise those procedures as necessary, and prepare to submit any required 510(k)s for modified devices. Public comments on the draft are due October 25, 2011, and should refer to Docket No. FDA-2011-D-0453.

The draft guidance does not include the decision-tree flowcharts that were included in the 1997 guidance. Rather, the new guidance provides a series of questions for manufacturers to address when evaluating device modifications in the following categories: (1) manufacturing process changes, (2) labeling changes, (3) technology or performance changes, and (4) materials changes. (The 1997 guidance does not address manufacturing process changes.) The guidance does not address combination products or nanotechnology-specific criteria. It also does not supplant existing device-specific guidances, such as the "Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses."

I. FDA Regulations on Modifying 510(k)-Cleared Devices

FDA regulations (21 C.F.R. 807.81(a)(3)) state that a new 510(k) must be submitted for a change or modification to an existing device when: (1) the change or modification "could significantly affect the safety or effectiveness of the device"; or (2) there is "a major change or modification in the intended use of the device."

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A. Changes that Could Significantly Affect Safety or Effectiveness

In determining whether a new 510(k) is necessary, the threshold question is whether a change *could* significantly affect the safety or effectiveness of the device. The draft guidance emphasizes that this question is different from determining whether a change actually *does* significantly affect safety or effectiveness. Although testing results submitted in a 510(k) application may demonstrate that a change does not affect safety or effectiveness, the guidance states that "[i]n most cases testing cannot … conclusively show that a change could not affect safety or effectiveness." Even changes intended as improvements to the device's safety or effectiveness could require submission of a new 510(k).

B. Major Changes or Modifications in the Intended Use

The draft guidance acknowledges that changes to a device's indications for use are not necessarily a change in its intended use; however, changes to the indications for use are generally "major" changes under 21 C.F.R. 807.81(a)(3) that could affect safety or effectiveness and therefore typically require submission of a new 510(k). If a device modification results in a new intended use, then the device will not be substantially equivalent (NSE) and likely will require submission of another marketing application (*e.g.*, approval of a premarket approval application (PMA), humanitarian device exemption (HDE), etc.).

II. Basic Principles

The updated guidance outlines several basic principles, some continued from the 1997 guidance, that manufacturers should follow in determining whether a new 510(k) is necessary:

- The modified device should be compared only to the most recently cleared version of the same device, as described in the 510(k) submission. The modified device should not be compared to a version of the device that has not received clearance. For example, if a manufacturer previously modified a device but determined that those modifications did not require submission of a new 510(k), the manufacturer should not rely on that device version as the comparator to determine whether a 510(k) is necessary for new modifications.

- The modified device should not be compared to any other device produced by the same manufacturer or another manufacturer, even if that device could be considered a predicate for the modified device. For example, a manufacturer should not conclude that a change in material for Device A does not require submission of a new 510(k) because that same material is incorporated in the company's 510(k)-cleared Device B or another manufacturer's cleared device. The decision to submit a new 510(k) for a modified device should not be based on whether the modified device is substantially equivalent to another device; rather, the decision should be based on whether the modification could significantly affect safety or effectiveness or reflects a major change in the intended use.

- Each change should be assessed *individually* and *collectively as a whole*. If any one change triggers the need for a new 510(k), all changes to the device since the last clearance should be described in the new 510(k), including changes that were implemented without submission of a new 510(k). The 510(k) submission should distinguish the specific change(s) that triggered the application.

- All modifications should be made in accordance with the Quality System Regulation (21 C.F.R. Part 820), unless the device is exempt from this regulation.

- Firms should have procedures in place for evaluating whether a proposed change to a device could significantly affect safety or effectiveness of the device or introduce a major change in the intended use. Firms also should document their determinations and the scientific justifications for why a new 510(k) is not needed for a device change, including answers to the specific questions listed in the new draft guidance.

III. Manufacturing Changes

Under 21 C.F.R. 807.81(a)(3), a new 510(k) is required for a significant change or modification in manufacturing process that could significantly affect the safety or effectiveness of the device. FDA's guidance identifies several manufacturing modifications that are likely to require submission of a new 510(k):

- If FDA's review of the cleared 510(k) included manufacturing information (*e.g.*, FDA generally expects 510(k)s for wound dressings to include manufacturing information);

- If the device was required to undergo a pre-clearance inspections (*e.g.*, infusion pumps);

- If the modification leads to a performance change (*e.g.*, measurement accuracy) or specification change (*e.g.*, tensile strength);

- If a sterilization change results in a sterility assurance level (SAL) less than 10^{-6};

- If there is a change in the sterilization method (*e.g.*, change from moist heat sterilization to e-beam sterilization); or

- If the device is changed from sterile to non-sterile, or vice versa.

The guidance specifies that changes to device packaging or changes to expiration dates for the use of a device are unlikely to require a new 510(k), as long as the changes are validated using the same or similar testing methods, as described in the prior 510(k) clearances.

IV. Labeling Changes

The guidance emphasizes that firms must consider more than the device's instructions for use in evaluating labeling changes because the statutory definition of labeling includes all written, printed, or graphic matter on or accompanying a medical device.[1] For example, the guidance notes that labeling may include "instructions that are displayed on a screen by software, stickers or text placed on a control unit, and promotional materials." FDA states that firms should analyze the following regarding labeling changes:

[1] Federal Food, Drug, and Cosmetic Act ("FDCA") § 201(m).

A. Indications for Use

Most labeling changes that affect the indications for use will require submission of a new 510(k). However, if a firm decides to remove or limit use within the cleared indications "*due strictly to marketing reasons*," then a 510(k) probably will not be necessary. For example, if a device was cleared for use with multiple indications, but the firm eventually decides to market the device for only one of the cleared indications due to changes in market demand, then FDA generally will not consider this to be a "major change" requiring a new 510(k). However, if the change in indications is made for non-marketing reasons (*e.g.*, in response to complaints or corrective actions), then a 510(k) likely will be required. Other common changes in indications that trigger the need for a new submission include:

- Changes that allow reuse of devices that were labeled as "single use only;"
- Changes from prescription to over-the-counter (OTC) use;
- Changes from prescription use in a clinical setting to use in a home; the 1997 guidance had stated that a new 510(k) clearance was not required to allow home use of a device that remained a prescription device and whose use in the home was accepted medical practice; and
- Changes from use in a general patient population to use in a specific patient population.

B. Contraindications for Use

FDA permits firms to make additions to contraindications, and then submit them to FDA in a 510(k) that is labeled "change being effected" (CBE). Manufacturers may market the device with the modified labeling, but FDA may request revisions after reviewing the 510(k).

A labeling change that deletes a contraindication is considered an expansion of the indications for use and should be submitted in a 510(k) submission prior to being implemented.

C. Instructions for Use

The guidance states that FDA generally will consider changes in the labeling that instruct the user to use the device in a different manner than described in the clearance to constitute major changes in the intended use of the device, and therefore require submission of a new 510(k). For example, modifying a device that provides diagnostic information to include additional or new instructions on how to interpret the device's data would be considered a "major change" requiring a new 510(k).

D. Warnings or Precautions

The addition of warnings or precautions generally will not require submission of a new 510(k). However, deletions of warnings or precautions are likely to require a new 510(k). FDA's 1997 guidance did not require new 510(k) notices to delete warnings or precautions.

V. Changes in Technology, Engineering, and Performance

The guidance states that firms should consider the following in evaluating technology, engineering, and performance changes:

- Changes to the fundamental scientific technology of the device likely will require a new 510(k) (*e.g.*, changing from analog to digital control).

- Changes in the type of power input or output from a device likely will require a new 510(k) (*e.g.*, changing from an external power source to a battery power source).

- Changes that have the potential to significantly alter the performance characteristics or specifications of the device likely will require a new 510(k) (*e.g.*, changing the sensitivity of a pulse oximeter from an oxygen saturation of 90% to 70%). The new 510(k) should include comparative testing that demonstrates whether the performance characteristics are improved or worsened with the change.

- Changes in the ergonomics or patient/user interface may significantly affect the safety or effectiveness of the device and therefore require a new 510(k). The guidance notes that changes intended to increase user comfort can have unintended consequences. For example, ergonomic changes to a surgical device that affect the central mechanical performance of the device will require a new 510(k).

- Depending on the device type and component being modified, changes in dimensional specifications could significantly affect safety and effectiveness and therefore require a new 510(k). For example, device dimensions that are modified beyond tolerance ranges usually will require a new 510(k). Historically, FDA has taken this position, even though it was not explicitly stated in the 1997 guidance. However, modifications within previously cleared size ranges typically will not require a new 510(k). The guidance recommends that the firm consult with the appropriate review divisions regarding any questionable dimensional changes.

- If a software change could expand the capability of the device, affect device performance, or impact a clinical algorithm, then a new 510(k) likely would be necessary. For example, if a firm modifies software that plans placement of an implant based on patient data to add a new patient parameter, then the firm should submit a new 510(k).

- Most changes that impact how a device receives, transmits, or displays electrical signals or data are likely to require submission of a new 510(k). For example, if diagnostic software that displays images on a monitor is modified to display images on a mobile handheld device, then a new 510(k) should be submitted.

- Changes that take control of the device away from the user or that assist or take away decision-making from a user are likely to require a new 510(k). For example, if colon imaging software is modified to include computer-assisted detection, then a new 510(k) should be submitted.

- Changes that address known or newly identified risks or failure modes of the device are likely to significantly affect safety or effectiveness and typically require new 510(k)s. These changes also may require a device recall. For example, adding a color-coded luer to prevent the misconnection of a feeding tube would require submission of a new 510(k).

- Technological or design changes can affect how a device is used in practice, even if there is no accompanying change in the indications. These changes may require new directions for use or a labeling limitation to address a potentially harmful off-label use of the device. A new 510(k) likely will be required for the following device modifications:

    - A change that allows a device to be used in a different or modified medical procedure, or to treat or diagnose a disease or condition that was not included in the previous clearance;

    - A change that allows a device to be used in a new, expanded, or more specific patient population than included in the previous clearance;

    - A change that alters an established medical procedure;

    - A change that allows a device to be used in a new environment associated with new risks, such as a at a doctor's office rather than in a hospital operating room;

    - A change that allows the device to be used by a lay person outside of a clinical setting (*e.g.*, home use), or changes a device from prescription to OTC;

    - A change that allows the device to provide new information or data to the user that could be used for patient assessment or diagnostic purposes, even if the new assessment information is used as an adjunct to other measures.

VI. Changes in Materials

In evaluating changes in materials, the guidance states that firms should first consider whether the material contacts the patient, either directly or indirectly. The guidance defines direct contact to include when "a material touches any tissue or bodily substance of patient while it is still in or on a patient." Indirect contact is when "a material has the *potential* to come into contact with any patient tissue or bodily substance by some intervening material (*e.g.*, liquid or gas) by first coming in contact with the intervening material, which subsequently comes in contact with the patient tissue or bodily substance." For example, a catheter hub is external to the patient, but the fluids and drugs infused through the hub directly contact the patient; therefore, the materials in the hub should be biocompatible. By contrast, although most implants contact patients directly, the internal contents of implants may not be patient-contacting if they are hermetically sealed so that there is no transfer of material within the device; therefore, the internal components would not need to demonstrate biocompatibility.

In general, material modifications that *cannot* have direct or indirect contact with the patient will not require a new 510(k), unless they affect the fundamental device technology or performance (*e.g.*, preservatives, antibacterials, structurally significant components, etc.).

Since changes in the material formulation (*i.e.*, chemical composition of the material and their physical chemistry) may affect the device's biocompatibility, material properties, or safe and effective performance, a new 510(k) should be submitted for these changes to patient-contacting devices or device components. Most material formulation changes of non-patient-contacting materials will not necessitate a new 510(k). The guidance highlights that material formulations can be affected indirectly by processing aids and contaminants that are not intended to be part of the material but are introduced by manufacturing, sterilization, or handling.

Changes to a device coating or surface modification technique, including chemical formulation, method of application, or surface preparation likely will require a new 510(k). As with changes in material formulation, residual contaminants can indirectly change the device surface and should be considered.

VII. Clinical Data to Support Substantial Equivalence

If a firm determines that clinical data are needed to assess the safety or effectiveness of a modified device, then a new 510(k) should be submitted. The potential exception is for in vitro diagnostic devices, which have different testing requirements. The guidance defines clinical data to include prospective, controlled clinical trials, as well as any data derived from human subjects.

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King & Spalding will continue to provide feedback to FDA regarding the types of changes that should or should not require new 510(k) clearance. In addition, King & Spalding will monitor whether FDA makes any substantive changes to this guidance before finalizing it, and to what extent, if any, the Agency applies this guidance before finalization. Please contact us if we can assist you in analyzing modifications to existing devices or in preparing comments on this draft guidance.