FDA Issues Draft Guidance on When to Submit a Premarket Notification Submission

By Lynn Tyler

Barnes & Thornburg’s Food, Drug & Device Update, Fall 2011

The FDA recently issued a draft Guidance to manufacturers on when to submit a premarket notification submission (510(k)) for changes or modifications made to that manufacturer’s previously cleared medical device. The draft Guidance explains the underlying principles that FDA uses to determine when a 510(k) is necessary for a modified device. When final, this draft will supersede the 1997 Guidance on the same subject.

The applicable FDA regulation, 21 CFR 807.81(a)(3), requires a new 510(k) for any change or modification that “could significantly affect” either the safety or the effectiveness of a device. Thus, this is the key issue addressed by the draft Guidance. The types of modifications addressed in the draft Guidance include, but are not limited to, manufacturing process changes, labeling changes, technology or performance specification changes, and materials changes.

To determine whether a device modification is significant and thus requires a new 510(k), a manufacturer should compare the modified device only to the most recently cleared version of that device (not to any other approved or unapproved device of the same or a different manufacturer) and decide whether the modification could significantly affect the safety or effectiveness of the device.

The draft Guidance poses several questions, summarized below, and offers general rules and examples in most instances. Further, the draft Guidance states that a manufacturer should answer the questions for each individual change (FDA’s emphasis) to its device until a decision is made either to submit a 510(k) or to document the change and the basis for concluding that it does not require a 510(k). For example, if a manufacturer changes the length of a device, the thickness of the device, and the material of the device, each of these three changes should be considered individually. Further, after assessing each change individually, manufacturers should assess all changes made since the last 510(k) clearance collectively to determine whether the collective sum of all changes triggers the requirement for a new 510(k) submission.

The major types of changes discussed and the general rules given are (with some editing) as follows:

1. Manufacturing Process Changes

Manufacturing process changes will be particularly important for devices where the manufacturing process information was reviewed in the original 510(k) submission. Generally, changes in device packaging or changes in the expiration date for use of a device do not result in the
need to submit a new 510(k). Changes in sterilization have the potential for changing the performance characteristics of a device. If these changes could significantly affect the safety or effectiveness of the device, the changes in sterilization methods trigger the requirements for a 510(k) submission. The draft Guidance offers specific rules for changes in sterilization ratings and methods.

2. **Labeling Changes**

The draft Guidance states that FDA views most labeling changes that affect the indications for use, whether made to a specific indications section of the labeling or not, as major changes to the intended use of a device that warrant the submission of a 510(k).

According to the draft Guidance, FDA recognizes that, in general, the addition of a contraindication based on new information is important to public health and should be implemented immediately. To facilitate the timely implementation of such changes, manufacturers are encouraged to add new contraindications to labeling of cleared devices and to notify existing device users of such contraindications as expeditiously as possible whenever a pressing public health need arises. The new labeling should be submitted to FDA as part of a new 510(k) that is prominently labeled “change being effected.” A change in the indications for use that removes certain indications or limits use within the currently cleared indication *due strictly to marketing reasons is not* a major change in intended use under 21 CFR 807.81(a)(3) that requires submission of a new 510(k).

Manufacturers planning to delete a contraindication should submit a new 510(k) prior to effecting the change because this type of labeling change expands the indications for use.

If the labeling change instructs the user to use the device in a different fashion from that originally cleared, then this could lead to new significant safety risks or less effective use of the device. FDA views changes of this nature as major changes in intended use that require submission of a 510(k).

According to the draft Guidance, the submission of a new 510(k) for labeling changes that add warnings or precautions is generally unnecessary; however, manufacturers are encouraged to discuss these situations with FDA. Labeling changes that delete warnings or precautions, however, could be changes in intended use that affect how a device is used and could therefore have a significant effect on safety or effectiveness. These changes are likely to warrant new 510(k) submissions.

3. **Technology, Engineering, and Performance Changes**

A new 510(k) submission should generally be submitted for modifications to device technology, engineering, and performance that significantly affect the cleared Indications for Use or fundamental technology of the existing device, or that substantially change the performance characteristics or specifications of the device.

All changes in fundamental scientific technology could significantly affect safety or effectiveness. Therefore, such changes require the submission of a new 510(k).

Changes in energy type are a change in design that will always have a significant effect on safety or effectiveness because power inputs and outputs are typically critical to proper device function. Most of these changes should be reviewed in a new 510(k) prior to marketing.
4. **Changes that have the potential to significantly alter the performance characteristics or specifications of the device**

Changes that have the potential to alter significantly the performance characteristics or specifications of a device potentially impact the safety and effectiveness of the device as well and a new 510(k) with comparative testing should be provided for such modifications, whether the performance characteristics are improved or worsened.

5. **Changes in ergonomics or the patient/user interface**

Changes of this type may significantly affect the safety or effectiveness of the device, but not all such changes do. The factors to consider in determining whether such a change requires submission of a new 510(k) are whether the change can expand how the device will be used or affect how it will perform.

6. **Dimensional changes**

Dimensional changes can, but do not always, significantly affect safety and effectiveness. FDA recommends that manufacturers consult the appropriate review division regarding any questionable dimensional change.

7. **Software changes**

The factors to consider in determining whether a software change requires a new 510(k) are whether the software change could expand the capability of the device or affect device performance. Such changes will likely warrant a new 510(k). Changes to device software that could affect a clinical algorithm (an algorithm that controls how software analyzes, interprets, or uses patient data) would also warrant a new 510(k).

8. **Changes to how the device receives, transmits, or displays electrical signals or data**

According to the draft Guidance, changes to how a device receives, transmits, or displays electrical signals or data have the potential to significantly impact safety or effectiveness by altering data communication quality and therefore should result in a new 510(k) submission.

9. **Changes to make controls autonomous**

Any device modification that takes control of the device away from the user or is used to assist or take away decision-making from a user likely introduces new risks that could significantly affect safety or effectiveness, and should be reviewed in a new 510(k) submission prior to marketing.

10. **Changes to address specific risks or failure modes**

Changes that are implemented to address either known or newly identified safety risks or failure modes of a device, including those intended to address a known device- or user-related adverse event or complaint, are by definition likely to significantly affect safety or effectiveness, even if the modification is intended to make the device more safe than the previous version.
11. Changes affecting how the device is likely to be used in practice

Technological or design changes may affect how a device is used in practice, and therefore affect the safety or effectiveness of the device, even if no change in the Indications for Use statement accompanies the change. Particularly when the modification could create a reasonable likelihood of off-label use that could cause harm, a new 510(k) should be submitted to allow FDA to determine whether a change to the labeling is necessary, even if the manufacturer does not intend a change to the indications for use in the labeling.

12. Materials changes

In general, material modifications to device components that cannot have direct or indirect contact with the patient do not significantly affect safety or effectiveness of the device and so do not require a new 510(k) submission, unless they affect the fundamental device technology or performance (e.g., preservatives, antibacterials, moving parts, structurally significant components, lubricants, etc.).

Changes in material formulation of patient-contacting devices or device components may affect the biocompatibility of the device. These changes may also affect material properties and the safe and effective performance of a device. Therefore, a new 510(k) should be submitted for changes in material formulation for patient-contacting devices or device components.

Changes to a device coating or surface modification technique, including chemical formulation, method of application, or surface preparation (e.g., acid-etching, blasting, etc.) generally significantly affect safety or effectiveness and would require a new 510(k).

13. Clinical data necessary to determine SE

A manufacturer’s determination that clinical data is needed because bench testing or simulations are not sufficient to assess the safety or effectiveness of a modified device is a sure sign that the modification could significantly affect safety or effectiveness and that a new 510(k) should be submitted.

14. Other Issues

The draft Guidance reminds manufacturers that whenever they change their device, they must comply with the Quality System (QS) regulation (21 CFR Part 820) unless the device in question is exempt from the QS regulation. This regulation requires that specification changes be documented, validated or, where appropriate, verified prior to their implementation.

Manufacturers should have a mechanism or standard operating procedures in place for evaluating whether a proposed change meets the regulatory threshold for a new 510(k). Once a manufacturer has fully considered the device modifications:

If there are multiple changes and analysis of any one of the changes results in a determination that submission of a new 510(k) is required, then the manufacturer should submit a 510(k) that incorporates all of the planned changes as well as a comparison of the changed device to the device as it was described in the most recently cleared 510(k). All changes to the device since its most recent 510(k) clearance should be identified, even those that did not trigger the need for a new 510(k); the specific change(s) that triggered the 510(k) should be distinguished.
If a manufacturer determines that its device modification(s) could not significantly affect safety or effectiveness and therefore decides not to submit a new 510(k), it should document the basis for concluding that it does not require a 510(k). Manufacturers should scientifically justify their conclusions that modifications, individually and collectively, could not affect safety or effectiveness. A copy of this documentation should be maintained See 21 CFR 820.30 and 820.70(b).

The full text of the draft Guidance is available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM265349.pdf and should be consulted for further detail. It is important to recall that even final Guidances are not “law,” but rather non-binding statements of FDA’s current thinking on a topic.

For more information about Barnes & Thornburg LLP’s Food, Drug & Device Law group, contact Lynn Tyler, Chair of the Food, Drug & Device Law practice group at lynn.tyler@btlaw.com or 317-231-7392; Nicolette R. Hudson at nicolette.hudson@btlaw.com or 614-628-1417; or Hae Park-Suk at hae.park.suk@btlaw.com or 202-408-6919.

Visit us online at www.btlaw.com.