FDA Issues Guidance on Submitting 510(k)s for Changes to Existing Devices

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On October 25, 2017, the Food and Drug Administration (FDA) issued a final guidance document, *Deciding When to Submit a 510(k) for a Change to an Existing Device*, which describes when a change in a medical device would require the submission of a new premarket notification (commonly referred to as a 510(k)). The guidance document updates and supersedes FDA's original guidance on the topic, dated January 10, 1997. The final guidance provides additional information on how to use a risk assessment to evaluate whether a change requires a new 510(k), gives specific examples of when a change might require a new 510(k), clarifies important terms, and makes recommendations on how to document decisions on whether to submit a 510(k).

The guidance document is limited to medical devices subject to premarket notification requirements that are modified or changed after FDA clears the 510(k) for marketing authorization. The guidance also applies to pre-amendments devices (devices that were in commercial distribution prior to May 28, 1976) and devices that were granted marketing authorization through the De Novo classification process. The guidance does not address changes to devices that are exempt from the premarket notification requirements (*i.e.*, "510(k)-exempt") or that require premarket approval. We are not including an exhaustive recitation of all the changes from the previous guidance document, and are, instead, providing a high-level overview.

Regulatory Background

Devices that are currently on the market and are subsequently changed or modified may require the submission of a 510(k) prior to commercial distribution, if the device is "about to be significantly changed or modified in design, components, method of manufacture, or intended use."[1] Under the regulations, the following constitute changes that require a 510(k) submission:

- A change or modification in the device that could significantly affect the safety or effectiveness of the device, *e.g.*, a significant change or modification in design, material, chemical composition, energy source, or manufacturing process; and
- A major change or modification in the intended use of the device.[2]

As noted in FDA's original guidance, interpreting these provisions can lead FDA and manufacturers to diverging conclusions. While preserving the basic format and the content of the original guidance, FDA's superseding guidance strives to provide further clarity to increase the consistency of interpretations of these provisions.

FDA uses qualifying words, such as "likely," because, as is the case with almost all FDA guidances, the guidance is not legally binding, and the agency cannot anticipate all possible changes manufacturers may want to make. However, companies should review the guidance as it represents FDA's current thinking. The guidance, similar to the 1997 version, employs flowcharts and text to help manufacturers through an FDA-recommended "logic scheme" to arrive at a decision whether to submit a new 510(k). The guidance provides a number of "guiding principles" to follow when using the flowcharts. These "guiding principles" are:

1 21 C.F.R. § 807.81(a)(3).
2 Id.

- If a modification is intended to significantly affect the safety or effectiveness of the device (*i.e.*, to significantly improve a clinical outcome), the submission of a new 510(k) is likely required;
- FDA's guidance, *Blue Book Memorandum K95-1, 510(k) Requirements During Firm-Initiated Recalls*, should be used if a device is modified to address a violation or recall;
- A manufacturer should first conduct a risk-based assessment to make an initial decision on whether a change could significantly affect the safety or effectiveness of a device;
- A manufacturer should consider whether a change could have any unintended consequences;
- 510(k) submissions are likely required when a risk-based assessment identifies any new risks or significantly modifies existing risks;
- If the risk-based assessment indicates a new 510(k) is not required, the decision should be confirmed by "successful, routine verification and validation activities," and, if any unexpected results surface, the decision should be reconsidered;
- Multiple changes or modifications should be assessed separately and in the aggregate;
- The risk-based assessment should compare the changed device to (i) the device as previously found to be substantially equivalent in the most recently cleared 510(k), (ii) the preamendment device, or (iii) a device that was granted marketing authorization through the De Novo classification process;
- If a 510(k) is submitted for a device with multiple changes, the submission should describe all of the changes that trigger the requirement for a new 510(k) submission;
- If a manufacturer makes several changes, but only one change triggers the 510(k) submission, the changes that do not require the submission may be immediately implemented, if they can be implemented independent of changes that do require a new 510(k); and
- Even if a manufacturer follows FDA's guidance and submits a new 510(k), a substantially equivalent determination is never assured.

FDA also advises that any change or modification to an existing device must comply with the Quality System Regulations (QSRs). Regardless of whether a change requires a 510(k) submission, the QSRs require manufacturers of finished medical devices to review and approve changes to device design and production.[3] In addition, manufacturers are required to document any changes and approvals in a master record, among other requirements.[4]

Flowchart Scheme

Distinct from the guiding principles, the logic scheme guides manufacturers through the recommended steps to arrive at a decision on submitting a 510(k). Instead of providing one large and daunting logic scheme, for ease of use, FDA broke down the logic scheme into six smaller sections, including:

- Main changes that might be made to a device;
- Labeling changes;
- Technology, engineering, and performance changes;
- Materials changes;
- Technology, engineering, performance, and materials changes for in vitro diagnostic devices (IVDs); and
- Considerations for risk-based assessments of modified devices.

First and most general, the flowchart covers the main types of changes that might be made to a device and guides manufacturers to the other five sections, as appropriate, to assess more specific changes. FDA advises that manufacturers should use each of the flowcharts, the guiding principles, the recommendations in each section of the

3 21 C.F.R. §§ 820.30, 820.70.
4 21 C.F.R. §§ 820.181.

guidance, and the examples provided in the appendix to the guidance in the decision-making process.

Labeling Changes

FDA notes that labeling changes "often pose the most difficult questions to be addressed by device manufacturers when deciding whether submission of a new 510(k) is required." The agency advises:

- A very subtle change in a label may have a very significant impact on the safety or the effectiveness of the device.
- Labeling changes should be evaluated with a focus on changes in indications for use and should also apply a risk-based assessment framework.
- Changes in the indications for use statement raise more concerns than any other aspect of device labeling.
- Most labeling changes that affect the substance, meaning, or scope of the indications for use could have a significant effect on safety or effectiveness, requiring a new 510(k).
- If a change merely clarifies the indication, and does not effect the meaning or the substance, a new 510(k) will likely not be required.

Technology, Engineering, and Performance Changes

Technology, engineering, and performance changes encompass a broad array of design activities and have their own separate flowchart. FDA provides the following guidance related to technology, engineering, and performance changes:

- A company should verify the change according to the QSR requirements, and, if the verification results raise any unexpected issues, a firm should reconsider a 510(k).
- Almost all changes to a control mechanism (which is the manner by which the actions of a device are directed) could significantly affect safety and effectiveness, requiring submission of a new 510(k).
- Submission of a new 510(k) will usually be required when there is a change to the energy output or input, but not if the only change is a change in the type of battery.
- If the change is to an IVD, the manufacturer should refer to the section of the guidance document specifically relating to IVD changes.

Materials Changes

Manufacturers considering materials changes should evaluate the other types of changes previously discussed and possible effect. For example, FDA notes that a material change might also lead to a change in the device label. Thus, the review should encompass all the related changes. Again, FDA states that if the materials change is to an IVD, the section that specifically addresses IVDs should be consulted. Among the questions to be asked when evaluating the need for a new 510(k) when there is a change in materials are:

- Is it a change in material type, formulation, or chemical composition?
- Is it a change in material processing or supplier?
- Does the changed material directly or indirectly contact body tissues or fluids?
- Has the new material been used in a similar legally marketed device?

Technology, Engineering, Performance, and Materials Changes for *In Vitro* Diagnostic Devices

FDA considers changes made to reagents or changes to a test method or protocol, among other things, as changes in technology, engineering, performance, or materials of an IVD. According to FDA:

- Manufacturers making such changes should also consider other types of changes, such as labeling changes.
- If a technology, engineering, performance, or material change alters the operating principles of an IVD, the change, in most cases, could significantly affect safety and effectiveness, requiring the submission of a new 510(k).

Submission of a 510(k), however, is not necessarily required for all changes that alter the operating principle of an IVD. If

result in modified performance reporting, FDA states that it will likely expect a new 510(k).

Considerations for Risk-Based Assessments of Modified Devices

The guidance document concludes with a number of considerations for the risk-based assessment of modified devices. Companies should review these with the logic schemes and flowcharts. FDA advises that the assessment should identify "all possible risks associated with the changed or modified device," including possible sequences of events, hazardous situations, and associated possible harms. Risks could include:

- Initiating hazards, failure modes, or circumstances;
- The sequences of events that could lead to a hazardous situation occurring;
- The likelihood of such situations arising;
- The likelihood that the hazardous situations lead to harm; and
- The nature of the harm that could result.

The assessment should then focus on risks that are supported by objective scientific evidence, and the severity and probability of the risk occurring. A number of approaches are listed in the guidance for estimating the probability of a hazardous situation occurring, including:

- Use of relevant historical and real-world data;
- Prediction of probabilities of risk using analytical or simulation techniques;
- Reliability estimates;
- Production data; or
- Use of expert judgment.

The use of multiple approaches "might serve to increase confidence in the results." If uncertainty exists, it may be useful to consider a qualitative approach. If it is determined that there is a negligible likelihood that a device change could result in harm, the agency notes that a new 510(k) is likely unnecessary.

AGG Observations

- While the guidance document and FDA's guiding principles serve as useful analytical tools, ultimately, whether a change or modification will require a new 510(k) submission is within FDA's discretion.
- Manufacturers and sponsors should use FDA's guidance document, including the logic scheme, guiding principles, and examples when determining if a device modification or change will require a 510(k) submission.
- If a company decides not to submit a new 510(k), it should document its decision in a memo to file. While FDA can disagree with the decision, such a written review and analysis demonstrates a good-faith attempt to comply and, perhaps, the agency may take a different enforcement approach

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