U.S. Food and Drug Administration Issues Final Guidance On Changes Related to Cleared Medical Device

After one false start, congressional intervention, a report to Congress and a relatively short interval between draft and final version of the guidance, the Food and Drug Administration (FDA) has issued its final guidance documents, *Deciding When to Submit a 510(k) for a Change to an Existing Device* (Oct. 25, 2017) (Final Guidance). The Final Guidance largely aligns with the well-worn 1997 guidance and the 2016 draft guidance, but companies should be aware of the differences and practical implications described below. The Final Guidance places a greater emphasis on changes made to a device’s overall risk profile and does not address changes to device software. Instead, FDA has issued a separate guidance document, *Deciding When to Submit a 510(k) for a Software Change to an Existing Device* (Oct. 25) (Software Changes Guidance) to describe the decision-making framework for software changes.

A complicated history. FDA first attempted to update its 1997 guidance (also entitled *Deciding When to Submit a 510(k) for a Change to an Existing Device* (Jan. 10, 1997) (1997 Guidance)) in 2011, by issuing the guidance *510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device* (July 27, 2011). Responding to strong opposition from industry, which claimed the guidance would have exponentially increased the number of 510(k) submissions, Congress took the extraordinary move of legislatively withdrawing the 2011 draft guidance in 2012. Congress further required FDA to issue a report to Congress on the subject of when a 510(k) is needed for a change to a marketed device. U.S. Department of Health and Human Services, *Report to Congress, Report on FDA’s Policy to Be Proposed Regarding Premarket Notification Requirements for Modifications to Legally Marketed Devices* (Jan. 1, 2014). FDA issued that report in 2014 and followed with a draft guidance that was better received on Aug. 8, 2016.

Similar approach to the 1997 Guidance. Despite the convoluted path to issuance of a final updated policy on 510(k) modifications, in several fundamental respects the Final Guidance closely tracks the 1997 Guidance. First, the central principle of the Final Guidance, like that of the 1997 Guidance, is based in regulation: namely, that a 510(k) premarket notification is required when a change or modification in the device “could significantly affect the safety or effectiveness of the device.” 21 C.F.R. §807.81(a)(3)(i)). FDA’s application of the regulation historically has been controversial. In the 1997 Guidance, FDA explained that the guidance should be applied “using the intended changes to devices.” FDA expands on this notion in the Final Guidance by explaining, “A change that is intended to significantly affect the safety or effectiveness of a device is considered to be a change that could significantly affect the safety or effectiveness.”
Guidance goes on to state that a modification that is not intended to significantly affect the safety or effectiveness should nonetheless be evaluated to determine if the change could have a significant effect. Thus, a submission will be required under the Final Guidance even if testing indicates that the modification does not significantly affect the safety or effectiveness of a device, so long as the change could and/or was intended to affect the safety or effectiveness. In addition, as with the 1997 Guidance, changes that could significantly affect safety or effectiveness by making the device significantly safer or more effective will require a new 510(k).

Second, labeling changes continue to be a focal point of the agency’s guidance. The Final Guidance follows the same general approach as the 1997 Guidance with respect to analyzing labeling changes but adds even more complexity to the decision matrix than was proposed in the 2016 draft guidance. As with the 1997 Guidance, the primary question with respect to labeling is whether the change affects the cleared Indications for Use statement. Further, the Final Guidance overtly applies the standard for changes that “significantly affect safety or effectiveness” so broadly as to subsume the second part of the regulatory standard for premarket notification, namely, whether a change constitutes “a major change or modification in the intended use” of the device under 21 C.F.R. § 807.81(a)(3)(ii). The Final Guidance provides that “most labeling changes that affect the substance, meaning, or scope of the indications for use could significantly affect safety or effectiveness and will require submission of a new 510(k).” The practical impact of this language and the Final Guidance’s flowchart for labeling changes is that unless the change falls into a few narrow exceptions, changes to the Indications for Use statement will require a new 510(k) regardless of whether they constitute a “major change or modification in the intended use.”

Under the Final Guidance, the following labeling changes will not automatically trigger a 510(k) requirement: (1) a change from a device labeled as reusable to a device labeled as single use, (2) a change from over-the-counter use to prescription use and (3) a change to the device name or solely to improve readability or clarity. The Final Guidance similarly clarifies that a change that could affect the directions for use of the device might not require a new 510(k) submission unless a risk-based assessment indicates otherwise.

Third, the 1997 Guidance explained that a manufacturer may be required to submit a new 510(k) when routine quality system design validation activities produce unexpected results or raise new issues of safety or effectiveness. The Final Guidance repeats this advice but takes it a step further. Under the Final Guidance, even when design verification and validation activities are conducted successfully and do not yield unexpected results, a manufacturer nonetheless likely will be required to submit a new 510(k) if a risk-based assessment reveals that a device modification could significantly affect safety or effectiveness.

**Important differences from the 1997 Guidance.** The Final Guidance document places an increased emphasis on risk management and uses the term “risk-based assessment” throughout to describe the analysis a manufacturer should perform when determining whether a modification could change the safety and effectiveness of the device. Under the guidance, FDA expects a manufacturer to take into account changes that could significantly affect the risks it presents in addition to those that could affect its safety and effectiveness. Although this point was implicit in the 1997 Guidance, FDA brought it to the fore in the recent guidance out of concern that common risk analysis methods define risk only in terms of effects on safety
(and not effectiveness). According to the guidance, a new 510(k) submission is likely required when a risk-based assessment of the modified device uncovers new risks or reveals significant changes to existing risks.

Another noteworthy change from the 1997 Guidance document is that the Final Guidance breaks out software modifications into a separate guidance that is intended to be a companion to the “main” 510(k) modifications guidance. The Software Changes Guidance contains the same threshold for submitting a new 510(k) for changes to an existing device, but the terminology differs to reflect the nature of software technology. The Software Changes Guidance contains a single flowchart to assess software changes and focuses on whether the change introduces a new/modified risk, or a new/modified risk control measure, that could result in significant harm. If the answer is yes, a new 510(k) likely is required. Changes that significantly affect clinical functionality or performance specifications also likely would require a new submission. The increased emphasis on risk analysis differs from the 1997 Guidance but is in alignment with the ISO 14971, “Medical Devices — Application of Risk Management to Medical Devices.”

When a manufacturer makes multiple changes that affect labeling or hardware in addition to software, the manufacturer should consult both guidance documents. If use of either guidance document leads to the conclusion that a new 510(k) should be filed, then a new submission likely will be required.

**Changes from the 2016 Draft Guidance.** The Final Guidance retains the structure and format of the 2016 draft guidance but includes important clarifications and modifications to the content. The Final Guidance clarifies that it applies not only to 510(k)-cleared and pre-amendment devices but also to other existing devices that are subject to 510(k) requirements, including nonexempt devices that were granted marketing authorization under the de novo classification process. A more subtle scope clarification in the Final Guidance relates to the applicability of the guidance to remanufacturers, such as reprocessors of single-use devices. Both the final and the draft explain that the guidance does not apply to remanufacturers of existing devices that do not hold their own 510(k). The Final Guidance, however, explicitly provides that the guidance applies to remanufacturers, including reprocessors of single-use devices, when the remanufacturer holds its own 510(k).

Perhaps of most significance to many device companies, FDA modified the labeling section of the draft guidance to include more changes. First, FDA changed the threshold question from whether there is a substantive change in the indications for use statement to whether there is any change in the indications for use. Secondly, the Final Guidance modified the inquiry of whether the labeling change affects the directions for use to whether the labeling change could affect the directions for use. Changes that could affect the directions for use, such as adding new instructions on interpreting data from a diagnostic device, may require a risk-based assessment. FDA’s rationale for this approach is that a labeling change that could affect the directions for use might also result in a change that describes a new disease, condition or patient population condition, even if that change is not reflected in the Indications for Use statement.

FDA departed from the draft or provided additional instruction on a number of other fronts in the Final Guidance. Some notable additions or changes:

- Not all changes to the type of joint, organ, bone, vasculature or tissue to which the device is applied or with which the device interacts will require a new 510(k).
• A new 510(k) will not likely be necessary for updates to methods or protocols that are made to reflect newly recognized consensus standards.

• Changes made to a device to increase user or patient comfort likely will not require a new 510(k) unless the modification affects the performance or functionality of the device.

• An infusion pump with inputs from other devices not previously described, such as a pulse oximeter or blood pressure monitor, should be evaluated as a modification that involves compatibility or interoperability with other devices, components or accessories.

• Any change in the chemical composition, manufacturing process, physical configuration or intended use of a material should be evaluated with respect to possible changes in biocompatibility.

• The risk-based assessment for some devices should take into consideration nonphysical injury, such as psychological harm.

• Manufacturers can use real-world data to estimate the probabilities of hazardous situations when assessing risk.

The new guidance documents do not fundamentally alter the agency’s approach to determining when modifications to a device will require a new 510(k) submission but do represent a shift away from rules-based decision-making to risk management. FDA will continue to expect manufacturers to submit a new 510(k) for significant labeling changes and for changes that introduce a new or significantly modified risk. Manufacturers should consult both guidance documents when making changes to the hardware or software of their devices.

If you have any questions regarding this Sidley Update, please contact the Sidley lawyer with whom you usually work or

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