When It's Time to Change, You've Got to Rearrange: FDA Issues Draft Guidance on When Changes to an Existing Medical Device Require a New 510(k)

Alan G. Minsk

Many of us remember the classic 1972 Brady Bunch song, "Time to Change," when Peter Brady sings (as his voice cracks), "When It's Time to Change, You've Got to Rearrange." Channeling its inner Brady, the Food and Drug Administration recently issued a draft guidance entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device."[1] The agency is soliciting comments and intends to hold a webinar in late August to further explain its position.

This Bulletin will not repeat, item-by-item, the contents of the voluminous document, which includes appendices and flowcharts. However, we will highlight certain parts of the draft that we believe are particularly noteworthy. We will also offer our observations at the end.

Regulatory Background

- According to 21 C.F.R. § 807.81(a)(3), a new 510(k) premarket notification is required when there are significant changes or modifications to an existing device. This may include: 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), or a major change or modification in the device's intended use.
- In January 1997, the agency issued a draft guidance, which stands today, to explain its interpretation of the regulation.
- This recently-issued draft, when finalized, will supersede the 1997 version.

Scope

- FDA explained that the draft does not apply to software changes or modifications, but it does apply to non-software changes to a device containing software or software that is a medical device by itself.
    - NOTE: FDA issued a separate draft guidance document on software changes or modifications.[2]
- The draft does not specifically address combination products, such as drug/device or biologic/device combinations, but the general principles and concepts described in the draft may be helpful to manufacturers in determining whether a 510(k) is necessary for changes to device parts of a particular combination product.
- The guidance is not intended to address whether 510(k) submissions are required from remanufacturers of existing devices who do not hold the 510(k) for the device (e.g., reprocessors of single-use devices).[3]

1 The document can be accessed at www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm514771.pdf.

2 See www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm14737.pdf

3 A remanufacturer is defined as "any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use."

"Guiding Principles"

- FDA offers "Guiding Principles" to industry to consider when evaluating whether a new 510(k) is needed. These general points are new from the 1997 draft guidance.
- If a manufacturer modifies a device with the intent to significantly improve the safety or effectiveness of the device (in response to a known risk or adverse event), a new 510(k) is likely required.
    - NOTE: changes that are not intended to significantly affect the safety or effectiveness of a device should, nevertheless, be evaluated to determine whether the change could significantly affect device safety or effectiveness, regardless of intent.
- A manufacturer should perform a risk-based evaluation to determine whether a change or modification could significantly affect the safety or effectiveness of a device:
    - review and evaluate all new risks and changes in known risks resulting from the device modification; and
    - if the company concludes that a new 510(k) is not required, the company should confirm its decision by successful, routine verification and validation activities.
        - NOTE: If routine verification and validation activities produce unexpected issues, FDA recommends a re-review of the prior decision.
- A manufacturer should consider whether there are any unintended consequences or effects of the device change:
    - e.g., changes in sterilization may unintentionally affect device materials, or changes to materials may unintentionally affect the device's performance.
- A company should consider hazards and hazardous situations, risk estimation, risk acceptability, risk control, risk/benefit analysis, and overall risk evaluation during the design and development of a medical device.
- A manufacturer should evaluate simultaneous changes individually and in the aggregate:
    - FDA recommends that, for each a time a change is made, a manufacturer should conduct a risk-based assessment that compares the changed device to the most recently-cleared device and the cumulative effect of the change.
- When a manufacturer changes a device, it should review if any action is needed to comply with an applicable Quality System Regulation.
- A 510(k) submission that is offered for a device with multiple modifications should describe all changes that trigger the requirements for a new 510(k), as well as describe other modifications since the last cleared 510(k), even if those individual changes did not require a new 510(k):
    - if a manufacturer makes multiple changes to a device, but only one change requires a new 510(k), the changes that did not require a new 510(k) may be immediately implemented, if those changes can be implemented independently of changes that do not require a new 510(k).

Guidance Usage

- FDA uses a "Main Flowchart," "Flowcharts" A through D, and examples to identify: (1) the main types of changes that might be made to a device; (2) labeling changes; (3) technology, engineering, and performance changes; (4) materials changes; (5) technology, engineering, performance, and materials changes for in vitro diagnostic devices (the previous two sections apply only to non-IVDs); and (6) considerations for risk assessments of medical devices.
- FDA includes appendices to: (1) provide specific hypothetical examples of changes to a device and whether or not a new 510(k) is required; (2) describe the type of documentation the agency expects a company to prepare if it concludes a new 510(k) is not required, for a particular change (all changes should be documented in an internal file so an FDA investigator or third party can understand the rationale for the decision);[4] and (3) explain

4 FDA provides examples of Regulatory Change Assessment formats.

definitions used in the draft.

- The agency makes clear that it cannot anticipate every type of potential change or offer guidance in all cases: "real-world device modification decisions will depend on the particular details of the change and the specific device in question."
- FDA intends that companies use the draft, with its explanations, examples, flowcharts, and appendices, as parameters for specific evaluation of particular device changes.

AGG Observations

- The revised guidance offers the medical device industry insights as to FDA's current thinking on when to submit a new 510(k) for changes to an existing device. It's not a one-size-fits-all document and, by the agency's acknowledgement, it cannot anticipate and answer all questions and permutations. Rather, by explaining its rationale behind certain types of changes and whether or not it believes a new 510(k) may (or not) be required, along with its appendices and flowcharts, FDA is attempting to provide industry with issues to consider.
- FDA's regulation is the first place to start. That's law. The guidance is an effort to further explain FDA's interpretation of that regulation. FDA cannot take enforcement against a company that fails to follow its guidance; it can take enforcement if the company fails to follow the regulation. However, by better understanding the guidance, companies get a peek of what FDA expects.
- A company that makes a change to an existing device should include members from its Medical, Quality, Regulatory, and Legal teams. Other groups, such as Manufacturing and Engineering, should be included as appropriate. Each member has unique experience, insight, and perspective, and all are important to evaluate whether a change might significantly affect safety, efficacy, or intended. For example, FDA's emphasis a company conducting risk-based evaluation, assessing whether the change was made in response to a safety or quality-related issue (e.g., Medical Device Report, recall) or unintended consequences or effects of a device change, all point to a collective involvement and decision-making process.
- A company may decide, based on the facts, that it is not required to submit a new 510(k). If such an assessment is made, it should document its rationale in a memo to internal file, including a review of FDA's regulations, the guidance document, a Health Hazard Assessment, and then applicability to the specific case. Someone from the company or outside the company, who did not prepare the memo, should review the document, with an objective and critical eye, anticipating where FDA or a competitor might challenge the position. FDA can always disagree with the decision but, if the company has a rhyme or reason for its good-faith interpretation, based on a careful review of FDA's rules and guidances, as well as a safety and risk evaluation, possible enforcement is minimized, although not necessarily eliminated. Any action taken by FDA might not be as severe as could be the case if no serious consideration was given to the change and its effect on safety, effectiveness, or intended use.
- We would add that, while not necessarily related to this guidance, we have seen cases where companies have submitted new 510(k)s for new uses, as an example, did not receive clearance, and proceeded with the sale of the new use anyway. While the mere submission of a new 510(k) is not an admission that a new application was needed, if a company chooses to submit, is rejected, and then markets the new use regardless, it should ask itself why -- did the company think the new 510(k) was not necessary, did it re-review FDA's guidance and come to a different conclusion, did the company not have the time to resubmit or collect the data FDA might have requested in the review, or was a senior management decision made to proceed at risk?
- Consider reviewing what other companies with similar products have done. That is, if all competitors are submitting new 510(k)s for changes similar to what your company is contemplating, this might suggest a new 510(k) should be provided. Of course, the fact that others made such a decision is not dispositive and does not mean that your company must submit a new 510(k). The guidance does not take this approach, and each case is different. However, if your company is alone in its belief, for example, that a new 510(k) is not required for a particular change and all other similar companies have concluded otherwise, your firm is on an island. This is merely a practical issue to consider.

- Finally, consider the what-ifs. What if, for example, the company does not submit a new 510(k) and something goes wrong with the change to the device, such as an injury or failure to work? Again, there are many cases when a new 510(k) for a change might not be required, and FDA acknowledges many such cases in its guidance. However, a firm must consider the potential consequences, such as liability exposure, FDA inspection, competitor challenge, loss of good will in the marketplace.

Authors and Contributors

Alan G. Minsk
Partner, Atlanta Office
404.873.8690
alan.minsk@agg.com

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Atlanta Office
171 17th Street, NW
Suite 2100
Atlanta, GA 30363

Washington, DC Office
1775 Pennsylvania Avenue, NW
Suite 1000
Washington, DC 20006

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