FDA Draft Guidance on Product Changes and the 510(K)

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“Device Validation Forum” discusses regulatory requirements, scientific principles, strategies, and approaches associated with medical device validation that are useful to practitioners. We intend this column to be a valuable resource for daily work applications.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator John E. Lincoln at jel@jelincoln.com.

KEY POINTS
The following key points are discussed:


• FDA holds the manufacturer responsible to make the 510(k) determination aided by this further clarification in the guidance. A table tracking and summarizing changes to a device is recommended.

• The draft’s listed categories of modifications that may require a 510(k) submission include changes to manufacturing process, labeling, technology, engineering, and performance, materials, or clinical data considerations.

• A possible format for documenting change analysis is presented.

INTRODUCTION
The US Food and Drug Administration issued the draft guidance 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device in July of 2011 in recognition of the need for further clarification of the FDA Blue Book Memorandum # K97-1, “Deciding When to Submit a 510(k) for a Change to an Existing Device” (January 10, 1997) and their two working group reports on 510(k)s and better science (August 2010 and January 2011). Currently, FDA is soliciting comments from stakeholders on the draft. When final, the revised document will supersede the January 10, 1997, K97-1 guidance.

While this is only draft guidance, it is useful to consider it in detail for the following reasons:

• The draft highlights areas that FDA thinks are most confusing or least in compliance by industry

• It illustrates FDA’s current thinking on the subject

• It outlines areas for further clarification and possible action, even while companies are still using the current K97-1 guidance for decision making

• It facilitates a more comprehensive change analysis or 510(k) submissions that proactively address these heightened FDA concerns

• It provides a vehicle for industry comments on the entire device changes analysis process (1).

CHANGES AND MODIFICATIONS
Device changes requiring a new 510(k) are the source of much confusion in industry. The 2011 draft guidance still states that FDA considers the manufacturer to be the best qualified to make such decisions. FDA still holds the manufacturer responsible to make the proper determination aided by this further clarification. FDA continues to require that the changes be tightly controlled (2). The analysis is to be documented and should include a written rationale for not submitting a 510(k). The draft guidance recommends a table (see Figure for one possible format) for tracking cumulative changes and their summarization. Generally, such analysis could be incorporated into a company’s engineering change order (ECO) or other
appropriate system when each is generated because of device changes.

If a number of evaluated and documented non-significant changes occur over the life of the device, a point is usually reached where the cumulative effects of the earlier changes and the newest change finally causes the manufacturer to decide that the device has been significantly changed, and that a new 510(k) is now required. Whenever a manufacturer decides to modify an existing device, they must then decide whether the proposed modification together with any previous non-significant changes require the submission of a new 510(k). FDA does not intend for every change to require a new submission, but that every change be evaluated as to the specific change and its cumulative effect with past changes since the last 510(k) submission. A standard operating procedure (SOP) should define this process, with defined decision points and rationale. The procedure should include the method of recording each change, decision rationale, and their documentation. All changes to a regulated device must be documented after each change.

A new, complete 510(k) application is required for changes or modifications to an existing device, where the modifications could significantly affect the safety or effectiveness of the device; or the device is to be marketed for a new or different “Indication for Use.” For a brief discussion of “Indications for Use” and “Intended Use,” see our discussion in the Winter 2011 issue of the Journal of Validation Technology. All changes in “Indications for Use” do require the submission of a new 510(k), because this changes the original 510(k) and its previous review emphasis.

All guidance and draft documents on how to decide when to submit a 510(k) for a change to an existing device are available from FDA’s Division of Small Manufacturers, International and Consumer Assistance (DSMICA), or may be obtained through the FDA website, www.fda.gov/cdrh, or by phone or fax.

Listed categories of modifications that may require a 510(k) submission include changes to the following:

• Manufacturing process
• Labeling
• Technology, engineering, and performance
• Materials
• Clinical data considerations.

**Manufacturing Process Proposed Change Considerations**

The guidance lists the following manufacturing process changes that should be considered:

• Was manufacturing information required as part of the original 510(k) submission? Factored in as part of the review? If yes = new 510(K)
• Was a pre-clearance inspection performed for original 510(k)? If yes = new 510(K)
• Changes in packaging or expiration dating do not generally require a new 510(k)
• Changes in sterilization that could affect device performance = new 510(k)
• If Sterility Assurance Level (SAL) becomes less than 10-6 = new 510(K)
• Changes in device sterility (i.e., non-sterile to sterile or sterile to non-sterile) = new 510(k) (1).

**Labeling Process Proposed Change Considerations**

Labeling changes are usually most difficult to evaluate because subtle changes can have profound effects on the safe and effective use of the device.

The draft guidance recommends consideration of the following, with most changes requiring a new 510(k):

• Does the change affect the indications for use? Changed especially for non-marketing reasons (e.g., complaints, corrective actions)?
• Changes that allow reuse of a previously labeled “single-use device”
• Changes from prescription to over-the-counter (OTC) use
• Changes from prescription use in a clinical setting to prescription home use
• Changes from general patient population to specific patient population
• Changes affecting the contraindications for use, including:
  • Adding a “true” contraindication: Add immediately but then submit new 510(k); may continue to market unless FDA says not to
  • Deleting a contraindication: Submit a new 510(k) before changing labeling and marking the new device, because this labeling change usually results in an expansion of “indications for use”
• Changes in “Instructions for Use” include the following:
  • If use is in a different fashion than before (new safety/effectiveness issues)
  • Is considered a major change in intended use
• Changes in “warnings” or “precautions” include the following:
  • Additions: Events causing such should be reported under MDR, 21 CFR 803; a new 510(k) is generally unnecessary (the draft recommends discussion with FDA though)
  • Deletions: Could be changes in intended use
and affect safety or effectiveness, and thus need a new 510(k)?

• “Other” labeling changes: Change in language clarification, aesthetic, or organizational or format, logo, name changes would not generally require a new 510(k) (1).

Technology, Engineering, and Performance Proposed Changes

The draft guidance lists the following changes that should be considered:

• All changes in fundamental scientific technology (design principle and method of application) require a new 510(k)
• Energy. Most changes in type of power inputs or outputs require a new 510(k), including from external power source to battery
• Changes that could significantly alter the performance characteristics or specifications of the device require a 510(k)
• Changes to ergonomics or the patient and user interface that expand how the device will be used or affect performance require a new 510(k). If only for comfort with no affect on S&E, then no 510(k) required
• Dimensional changes may or may not require a new 510(k). Is safety or effectiveness affected? Does the change cause the device to exceed dimensions, and tolerance ranges, listed in current 510(k)?
• Changes in software or firmware usually require a new 510(k). Consider the following:
  • Does it expand the capability of the device
  • Does it affect device performance
  • Does it affect a clinical algorithm (i.e., in analysis, interpretation, utilization of patient data)
  • Changes that impact receipt, transmission, or displays of electrical signals or data will almost always require a new 510(k). See FDAs guidance on “Deciding When to Submit a 510(k) for a Change to and Existing Wireless Telemetry Medical Device”
  • Changes that add an aspect of autonomous or semi-autonomous control to the existing device would require a new 510(k); control or decision-making is taken away from the user; can introduce false positives or negatives that could adversely affect the course of treatment
  • Changes to address a specific risk or failure mode, adverse event or complaint, by definition affect safety or effectiveness and require a new 510(k)
• A new 510(k) is definitely required if the above change(s) could encourage “off-label” usage that could cause harm
• Changes likely to alter or expand the use of the device (e.g., procedures, medical conditions)
• Changes that would allow the use of the device in a new, expanded, or more specific patient population (e.g., in pediatrics)
• Changes that significantly change or alter an established medical procedure associated with the device; Definitely if the above change could encourage “off-label” usage that could cause harm
• Changes intended to allow the use of the device in a new environment (with new S&E risks)
• Changes to allow the device to be used by a layperson outside of a clinical setting (e.g., prescription home-use, OTC)
• Changes allowing the device to provide new information or data for patient assessment or diagnostic purposes; even if merely an “aid” or “adjunct” to existing measures, or even if it is only “additional” information would require a new 510(k) submission (1).

Materials Change Proposed Considerations

The draft guidance lists the following changes in materials that should be considered:

• Does the materials change require other changes mentioned above (e.g., in labeling); such collateral changes are to be considered first to make the determination as to the need for a new 510(k)
• Consider: Changed material(s) patient contact, either directly or indirectly (e.g., device materials which contact contents which contents in turn then contacts patient)
• Change in material formulation and possible reaction to processing steps (e.g., manufacturing materials, sterilization, handling requirements)
• Changes involving the device surface (e.g., coatings, surface modification techniques); residual contaminants; new cleaning or removal issues. Most of the above would affect safety and efficacy, and hence require a new 510(k) (1).

New Clinical Data Requirements Proposed Considerations

The draft guidance states, “if bench testing or simulation are not sufficient to assess safety and effectiveness (S&E), the need for clinical data is a sure sign that the change or modification could significantly affect S&E (not necessarily true of in vitro devices—contact the appropriate review division within the Office of
Device Validation Forum.

Figure: 510(k) change analysis matrix per draft guidance.

510(k) CHANGE ANALYSIS

1. Narrative (Descriptions, Reasons, Cumulative …)

2. Decision Matrix
   2.2 Matrix:

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Manufacturing Process Changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Info required in orig?</td>
<td>N</td>
<td>No mfg. process information previously submitted.</td>
</tr>
<tr>
<td>2</td>
<td>Pre-clearance insp’n?</td>
<td>N</td>
<td>No previous pre-clearance inspection performed.</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Labeling Changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Indications for Use</td>
<td>N</td>
<td>“Indications for Use” not affected.</td>
</tr>
<tr>
<td>2</td>
<td>Reuse of a SUE</td>
<td>N</td>
<td>No reuse of a single use device.</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Technology, Engineering and Performance Changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Fundamental science</td>
<td>N</td>
<td>No changes in fundamental scientific technology.</td>
</tr>
<tr>
<td>2</td>
<td>Energy</td>
<td>N</td>
<td>No change in power input</td>
</tr>
<tr>
<td>3</td>
<td>Perform. characteristics</td>
<td>N</td>
<td>No change in performance characteristics / specifications.</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Materials Changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Change affect above?</td>
<td>N</td>
<td>Material change does not affect any other category.</td>
</tr>
<tr>
<td>2</td>
<td>…</td>
<td>…</td>
<td>…</td>
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<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td></td>
<td>Clinical Data Required?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Bench test’g insuff.</td>
<td>N</td>
<td>Bench testing / simulation testing sufficient for S&amp;E.</td>
</tr>
<tr>
<td>2</td>
<td>Clinical data necessary</td>
<td>N</td>
<td>No clinical data required to prove S&amp;E.</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

End of Device Change Decision Matrix

[Partially filled out as an example; to be filled out as appropriate]

3. Conclusion

4. Approvals

   Analysis Performed By: __________________________ Date: ____________

   Verified By: __________________________ Date: ____________
IVD)” (1). Clinical data is defined in the guidance as controlled clinical trials and any data derived from human subjects.

Like previous guidance on this subject, the basic issue for a determination that a new 510(k) submission is required is any modification to a device that could significantly affect safety or effectiveness, or any change in indications for use or intended use.

The basis for the decision the company makes as to whether to submit or not submit must be documented by the company, with the supporting data maintained by the company or manufacturer (e.g., in the product’s design history file, device master record file, or in a change control file keyed to the applicable product).

Each 510(k), whether for an original device, or for a modification(s) to an existing device, must be a stand-alone and complete document, including all information required of an initial submission. As discussed in our previous column on this subject, there is no “update” to an existing 510(K) (3). This also includes the two new, shortened versions of 510(k) submissions, discussed in a previous “Device Validation Forum” discussion (4). As discussed in that article, a “Special” or the “Traditional 510(k)” would be the submission of choice for changes to a device warranting a new 510(k) submission.

In our previous column’s discussion of device changes, we presented a possible change analysis matrix, based on the current guidance, the K97-1 Memorandum (3). That is still the operable guidance and suggested format to continue using, until this draft guidance becomes the final guidance. However, the following is a suggested format based on the draft, for consideration, and possibly for use as a “supplement” or “addendum” to the K97-1 analysis matrix, to further document such analysis.

**510(K) CHANGE ANALYSIS—POSSIBLE FORMAT**

The figure describes a possible format for documenting change analysis. Once performed, the analysis should be filed and cross-referenced to the product’s DHF, or device master record (DMR), or change history file, in accordance with defined company policy. This document must be readily available and able to be quickly retrieved.

As discussed in the previous column, there must be an appropriate “trigger” for the analysis for this system to be effective. Such a trigger may already exist. Some companies use their change order (CO, ECO) form to include a “510(k) required?” check box. This or similar trigger may need a slight modification to include reference to the completing of an analysis. It should be subject to quality assurance or regulatory affairs review if filled out by another function (e.g., engineering department).

**SUMMARY**

While the decision of when to file a new 510(k) on a changed product that has a previously cleared 510(k) by the same company is left to the manufacturer, the 2011 draft guidance underscores FDA’s expectations for such changes. The company must maintain a good review process for each change, and then make a good faith well-documented effort to make the determination whether or not to file as a result of the most current change.

The process should be defined, documented, and implemented in such a way that designated company personnel can readily, conscientiously, and consistently apply the analysis. Company personnel or others with a similar background must be able to defend the analysis to a representative of FDA (or in a court of law). Such a defense may be required months, if not years, later. The documentation and rationale must be presented in sufficient detail to allow others to provide such an explanation and defense.

**REFERENCES**

1. FDA, Draft Guidance 510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device, FDA, July 2011.

**ARTICLE ACRONYM LISTING**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPA</td>
<td>Corrective and Preventive Action</td>
</tr>
<tr>
<td>CDRH</td>
<td>Center for Devices and Radiological Health</td>
</tr>
<tr>
<td>DHF</td>
<td>Design History File</td>
</tr>
<tr>
<td>DHR</td>
<td>Device History Record</td>
</tr>
<tr>
<td>DMR</td>
<td>Device Master Record</td>
</tr>
<tr>
<td>DSMICA</td>
<td>Division of Small Manufacturers, International and Consumer Assistance</td>
</tr>
<tr>
<td>IVD</td>
<td>In Vitro Diagnostics</td>
</tr>
<tr>
<td>N/A</td>
<td>Not Applicable; Non-Applicable</td>
</tr>
<tr>
<td>NSE</td>
<td>Not Substantially Equivalent</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-The-Counter; Non-Prescription</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality Management System</td>
</tr>
<tr>
<td>RA</td>
<td>Regulatory Affairs</td>
</tr>
<tr>
<td>S&amp;E</td>
<td>Safety and Effectiveness</td>
</tr>
<tr>
<td>SE</td>
<td>Substantial Equivalence</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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