FDA Insight on the 510(k) Modifications Guidance

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Agenda

- Background on 510(k) device modifications
  - Current policy overview
- Development of draft guidance documents
  - FDA's goals
- General guidance highlights
- Software guidance highlights
- Next steps

510(k) Device Modifications Background

- Medical device innovation cycle requires continual modifications
  - Changes to 510(k) devices already cleared for marketing

- FDA's policy has two goals:
  1. Ensure patients and providers have timely access to modified devices
  2. Provide effective public health oversight of modified devices

Current Policy Overview

- 21 CFR 807.81(a)(3)
- Original *Deciding When to Submit a 510(k) for a Change to an Existing Device* guidance, K97-1
  - No change in interpretation or use of guidance
  - Will remain in effect until draft guidances finalized
- Quality System regulation (21 CFR 820)
- Device-specific guidance documents
- Special 510(k)s

When a 510(k) is Required for a Change

- 21 CFR 807.81(a)(3): The device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be *significantly changed or modified in design, components, method of manufacture, or intended use.*

- The following constitute significant changes or modifications that require a premarket notification:
  - (i) 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.
  - (ii) A major change or modification in the intended use of the device.

Original *Deciding When to Submit*, K97-1

- Issued January 10, 1997
- Flowchart-based model
  - Labeling, Technology, Materials, IVD Materials
- Flowcharts follow from key "Assumptions/Axioms"
- Relied on both the Quality System regulation (21 CFR 820) and device-specific guidances

Quality System Regulation

- 21 CFR 820.30(i) *Design changes* - Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.
  - Robust documentation is helpful to both FDA and manufacturers

Device-Specific Guidances

- Some guidances have modifications information specific to a device type
- Intended to build on general guidance
- FDA plans to include modifications info more routinely in device-specific guidances
- Current examples:
  - Pulse oximeter guidance
  - Contact lenses guidance

Special 510(k)s

- Appropriate when:
  - Indications for use unchanged
  - Fundamental scientific technology unchanged
    - No detailed testing
  - See FDA's 510(k) Paradigm guidance (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm)

Development of Draft Guidances

- Based on stakeholder feedback:
  - 2009 CDRH 510(k) Working Group Report
  - 2011 510(k) Device Modifications Guidance
  - 2013 Public Meeting
  - 2014 Report to Congress
- Consensus around retaining the basic paradigm of K97-1:
  - No paradigm changes in guidance
  - Clarification needed in certain areas
  - Risk management, reliance on Quality System regulation (21 CFR 820) where possible

Draft Guidance Goals

- Targeted changes to K97 guidance:
  - Clarity, including interpretation of key terms such as “could significantly affect”
  - Flowcharts – matched with text
  - Key principles
  - Materials changes
  - More examples
  - Recommendations on documentation
- Separate software guidance
- FDA may make greater use of device specific guidances to communicate modifications info

Deciding When to Submit a 510(k) for a Change to an Existing Device; Draft Guidance for Industry and FDA Staff

Published: August 8, 2016

General Guidance Scope

- Includes legally marketed devices subject to 510(k) requirements
  - Excludes PMA devices and 510(k)-exempt devices
- Software:
  - Does not apply to software-specific changes
  - Does apply to non-software changes to software devices or devices containing software (e.g., labeling)

- *Comment: how to evaluate multiple changes when some involve software, some don't?*

Evaluating Software and Non-Software Changes

- Software Modifications Guidance covers software revisions
- Other changes covered by General Modifications Guidance
- For example:
  - To add a new mode to software device (no hardware), use Software Mods. Only need to use General Mods for labeling revisions (e.g., to explain new mode)
  - To add a new mode to an infusion pump, use Software Mods for the software revisions and General Mods for the change to pump specifications

Guiding Principles
(Applies to both 510(k) Modification Draft Guidances)

- Referred to as “Assumptions/Axioms” in K97-1
- Essential principles necessary for use of both guidances
- Should be used in concert with rest of guidances
- *Comment: Generally positive feedback, with several specific comments*

Guiding Principles

- Modifications made with intent to significantly affect safety or effectiveness of a device
  - Per 21 CFR 807.81(a)(3)(i), a change that could significantly affect safety or effectiveness requires a 510(k)
  - Change that's intended to significantly affect safety or effectiveness (e.g., to address adverse events) requires a 510(k)
  - Changes not intended to significantly affect safety or effectiveness should still be evaluated through this guidance

Guiding Principles

- "Could significantly affect" and the role of testing
  - Risk-based assessment should be used to make initial determination of whether a 510(k) is necessary
  - Risk-based determinations not to submit should be confirmed by verification and validation (V&V)
    - If V&V activities produce unexpected results, decisions not to submit should be reconsidered

- *Comment: what are "routine" V&V and "unexpected results?"*
- *Comment: what if testing shows change doesn't affect, or that change has positive effect?*

Guiding Principles

- Unintended consequences of changes
  - Manufacturers should consider whether there are unintended consequences of device modifications
  - Example: sterilization changes may affect device materials
  - Example: dimensional change intended to increase strength may affect mating with other device components

Guiding Principles

- Use of risk management
  - Plays a central role in determining when a change "could significantly affect" safety or effectiveness
  - Draft guidances intended to leverage manufacturers' existing risk processes to determine when change requires a 510(k)
  - Because 21 CFR 807.81(a)(3)(i) requires 510(k) for change that "could significantly affect safety or effectiveness," both safety and effectiveness should be considered

- *Comment: terminology inconsistent and conflicts w/ISO 14971*

Guiding Principles

- Evaluating simultaneous changes
  - Changes should be assessed separately, as well as in aggregate
- Appropriate comparative device and cumulative effect of changes
  - To determine whether changes "could significantly affect safety or effectiveness," manufacturer should compare modified device to most recently cleared device
- *Comment: What about comparisons to other cleared devices?*
  - For purposes of determining whether a 510(k) is necessary, changes should not be compared to other predicate devices (this is not a substantial equivalence (SE) determination)

Guiding Principles

- Documentation requirement
  - Quality system regulation requires documentation of design changes
- 510(k) submissions for modified devices
  - When a 510(k) is required, 510(k) should describe all changes that trigger the requirement
  - Changes that do not trigger the requirement should also be described, if they would have been described in the original 510(k) for that device
  - Example: labeling changes should be described, even if they do not trigger 510(k) requirement, to ensure complete understanding of changes for a substantial equivalence (SE) comparison
- Following this guidance does not ensure SE determination

How to Use The 510(k) Modification Draft Guidances

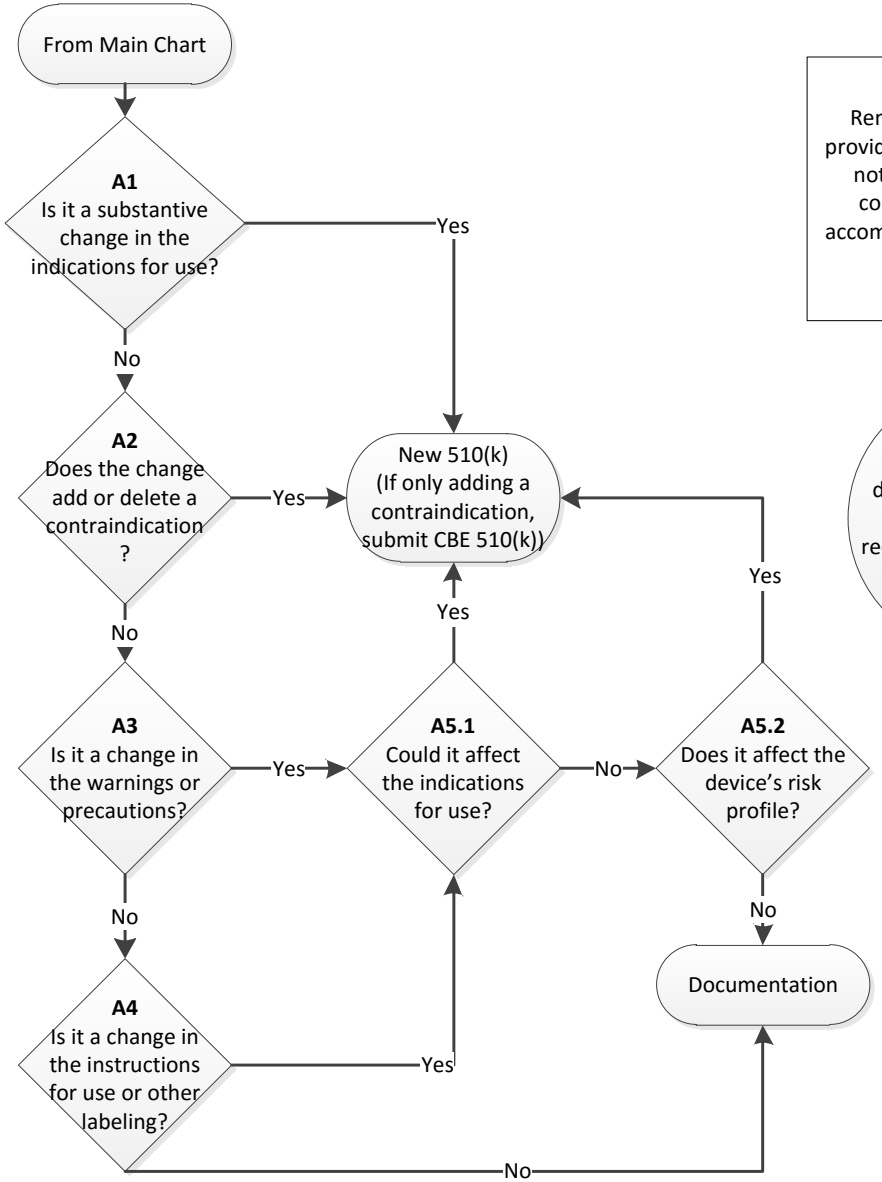
- Guidance describes a logic scheme for determining when a 510(k) is required

- Includes flowcharts for ease of use

Reminder: Flowcharts are provided as a visual aid, but do not capture all necessary considerations. Refer to accompanying text when using this flowchart.

Refer to Section E as directed by the text for additional recommendations on use of risk assessment.

Labeling Changes



Reminder: Flowcharts are provided as a visual aid, but do not capture all necessary considerations. Refer to accompanying text when using this flowchart.

Refer to Section E as directed by the text for additional recommendations on use of risk assessment.

Labeling Changes

- Focuses on changes to indications for use, and changes to other pieces of labeling that could affect indications for use
  - Describes common indications changes that likely do/don't require 510(k)s
  - Describes indications changes that depend on various factors, and provides factors to consider
    - Example: For changes in use environment, consider whether the device user changes, whether the environment presents different challenges such as a lower level of cleanliness, etc.

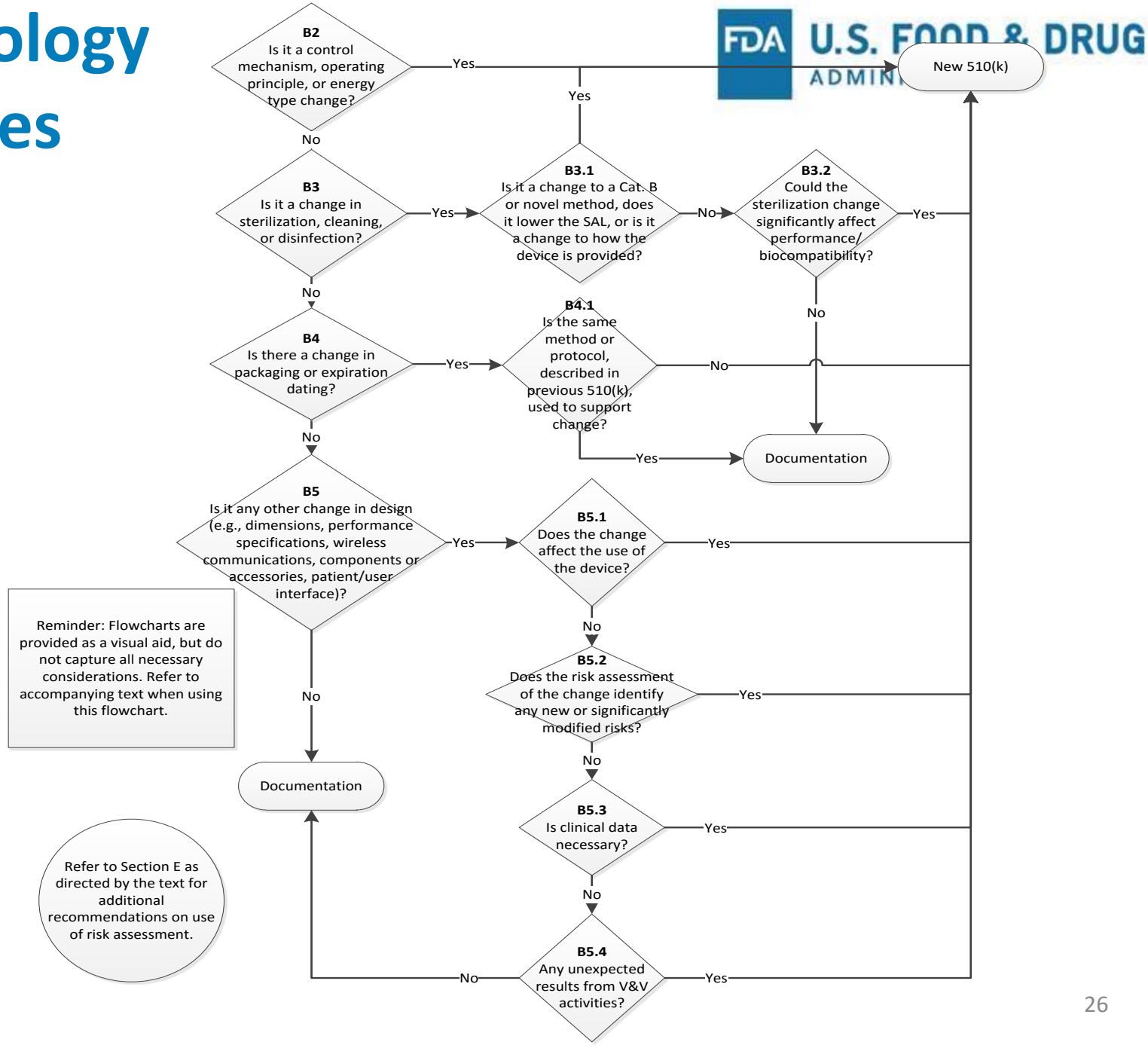
- For labeling changes that could not affect the indications for use, does a risk assessment identify any new or significantly modified existing risks?

Comments: Labeling Section

- Intended Use vs. changes to Indications for Use
  - New intended use would be NSE
  - Rather than refer to intended use, K97 and draft guidance refer to changes that have major impact on intended use, including certain indications for use changes

- K97 started with "Does the change affect the indications for use?"
  - Language was overly broad and lacked context
- Draft introduced "substantive" to provide clarity and introduced risk-based factors to consider to determine what changes are "substantive"
  - Bottom line: this is a risk-based assessment
  - Final guidance will clarify this particular point, and further explain how to apply risk-based assessment to changes that may or may not need a 510(k)

Technology Changes



Technology, Engineering, and Performance Changes

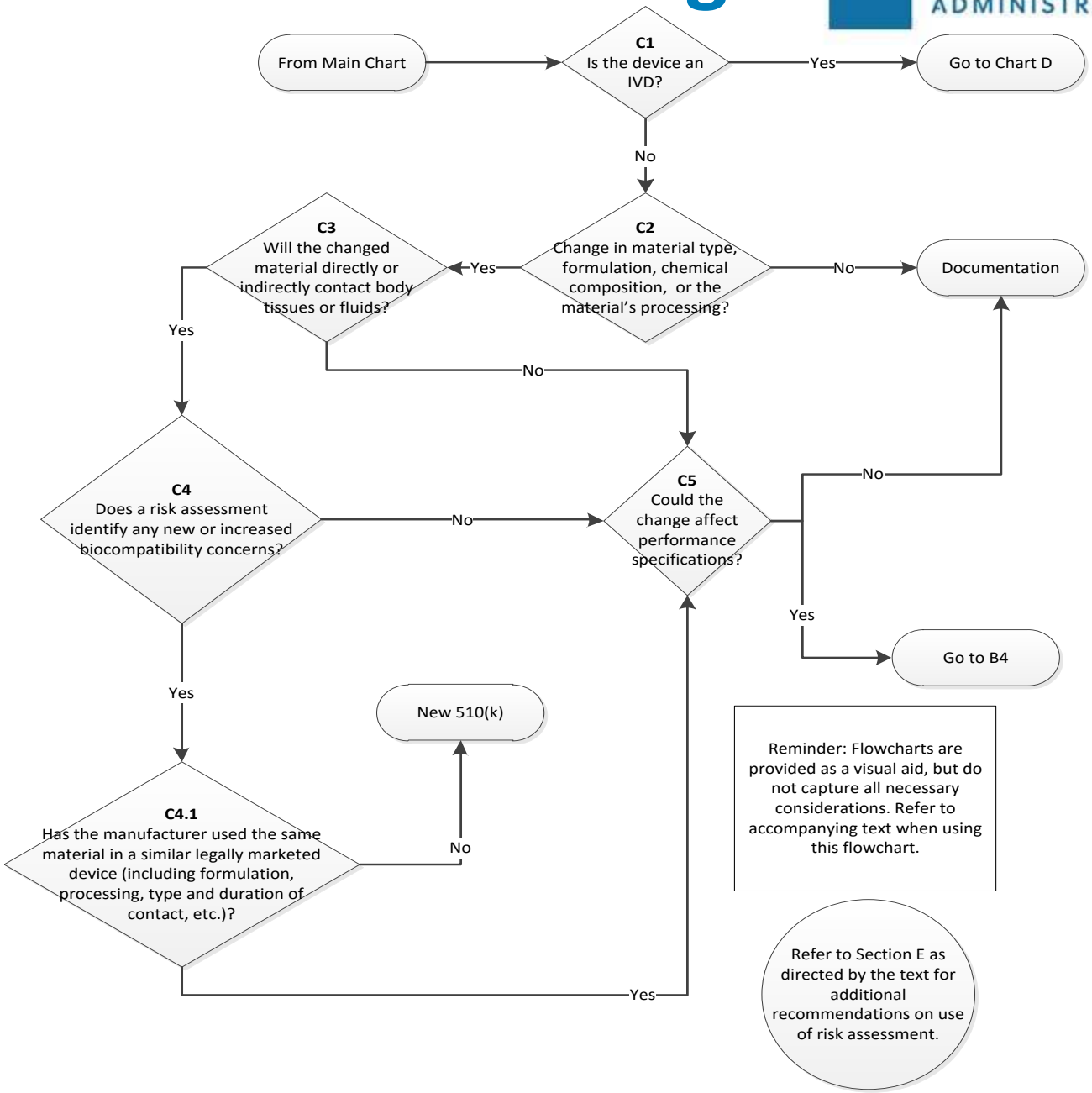
- Begins with recommendations on a few specific changes:
  - Fundamental device changes that almost always require 510(k)s, such as operating principle changes
  - Sterility and packaging changes, which depend on described factors

- For all other technology changes:
  - Does the change affect the use of the device?
  - Does risk assessment identify new or significantly modified existing risks?
  - Is clinical data necessary?
  - Any unexpected results from V&V activities?

Comments: Technology, Engineering, and Performance Section

- Additional clarity needed to explain "routine" V&V and "unexpected issues" that occur during V&V
  - Concept from K97
  - "Routine" refers to V&V activities used on version of device
  - "Unexpected issues" refers to changes to V&V activities driven by modification, e.g., new test method or new acceptance criteria

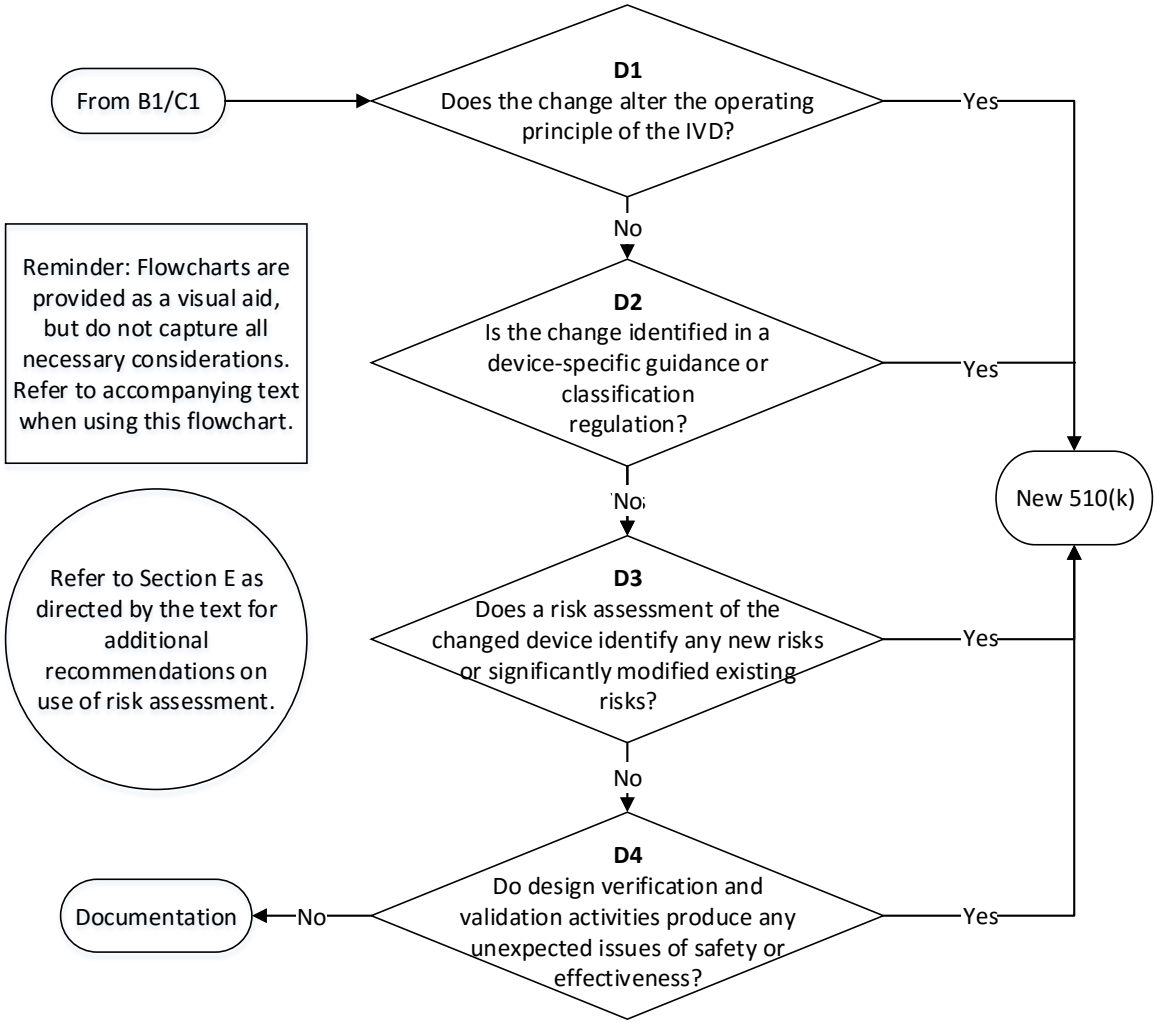
Materials Changes



Materials Changes

- Focuses on risk assessment of material changes
  - Does the new material have new or increased biocompatibility concerns compared to the unmodified material?
  - If so, has manufacturer used same material previously in a similar device?
    - If yes, manufacturer may be able to determine the new material could not significantly affect safety or effectiveness
    - If no, a 510(k) is likely required
- *Comment: what is a "similar device?"*
- If there are no new or increased concerns, or material doesn't have direct/indirect contact, could the change affect device performance?
  - If so, evaluate as technology change

Technology, Engineering, Performance, and Materials Changes for IVDs



Technology, Engineering, Performance, and Materials Changes for IVDs

- Modifications to IVDs other than labeling are handled in an IVD-specific section
- Analysis is similar to that found in non-IVD Technology and Materials sections, but is tailored to use language relevant to IVDs in explaining how decision should be made for IVDs
  - Focuses on risk assessment and changes that can affect IVD performance
- Guiding Principles, Labeling, and Risk Assessment sections also apply to IVDs

Considerations for Risk Assessments of Modified Devices

- Provides general recommendations on how to utilize risk assessment to evaluate device modifications
  - Thought process to consider changes not directly addressed by the guidance
  - Based on principles of ISO 14971 and CDRH benefit-risk guidances
- Risk likelihood or probability (*could* the change affect?)
  - If it's determined that the likelihood of a risk occurring due to a change is negligible, that change probably could not significantly affect safety or effectiveness
- Risk severity (could the change *significantly* affect?)
  - New risks, changes in risk acceptability or risk score, and duration of risk should be considered to determine if risk is significant

Considerations for Risk Assessments of Modified Devices

- Effectiveness concerns should also be considered
  - 21 CFR 807.81(a)(3)(i) requires 510(k) for change that "could significantly affect safety or effectiveness"
  - Therefore, manufacturers should consider the possible effects modifications may have on device effectiveness
    - What's the likelihood or probability that a change will affect device effectiveness?
    - If the change could affect effectiveness, could that affect be significant?
  - Consider the criticality of the device feature (labeling/design aspect/material/etc.) being modified
    - If a feature is critical to the effective operation of the device, changing it is more likely to be significant

Comments: Risk Assessment Section

- Describe “new or significantly modified risk” earlier in guidance
- Draft guidance talk about “physical injury or damage;” what about psychological injury?
- Use consistent language throughout guidance

Appendix A: Examples

- Appendix A includes hypothetical examples intended to illustrate process of determining whether a 510(k) is required
- Each example includes an explanation of why it would/wouldn't require a 510(k)
- Important to note: examples can't account for every possible detail and are not intended to be definitive

Appendix A: Examples

1. **Change:** The grip portion of a diagnostic ultrasound transducer is redesigned to improve user comfort.

   Relevant questions:

   B4 – *Is it any other change in design (e.g., dimensions, performance specifications, wireless communication, components or accessories, or the patient/user interface)?* Yes. This is a change to the device's user interface.

   B4.1 – *Does the change significantly affect the use of the device?* No. In this example, the redesign of the grip would not significantly affect the use of the device.

   B4.2 – *Does a risk assessment of the changed device identify any possible new or significantly modified risks?* No. Although the change to the transducer grip could affect certain risks, such as the user potentially mishandling the device, the severity of these risks for this device is low. (Note that mishandling a device such as a surgical instrument, however, would produce more severe risks, and could possibly lead to a new 510(k) being required.)

   B4.3 – *Are clinical data necessary to evaluate safety or effectiveness for purposes of design validation?* No. The manufacturer determines clinical data are not necessary for their specific change. They make the initial decision at this point to document the change to file.

   B4.4 – *Do design verification and/or validation activities produce any unexpected issues of safety or effectiveness?* No. In this example, routine verification and validation activities are conducted successfully.

   Decision: Document the change to file.

Appendix B: Documentation

- Most 510(k) devices must comply with Quality System regulation, which requires documentation of design changes prior to implementation
- Documentation is particularly important when manufacturers determine a 510(k) is not required
- Appendix B recommends basic elements of good documentation that every manufacturer should use
  - Also provides examples of documentation that can be adapted to the complexity of a given change (manufacturers can use these or adapt these as needed)

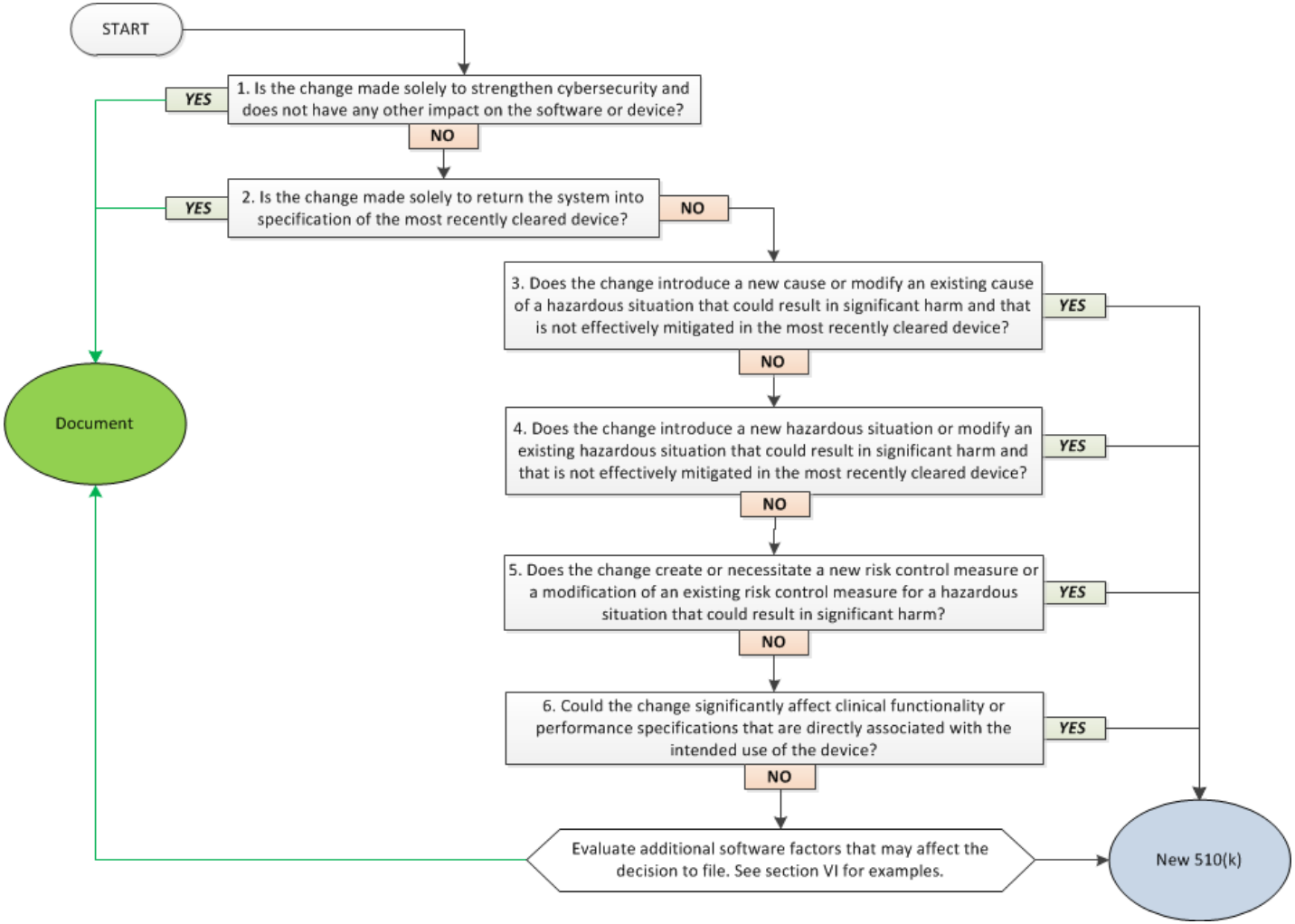
Deciding When to Submit a 510(k) for a Software Change to an Existing Device;
Draft Guidance for Industry and FDA Staff

Published: August 8, 2016

Guidance Scope

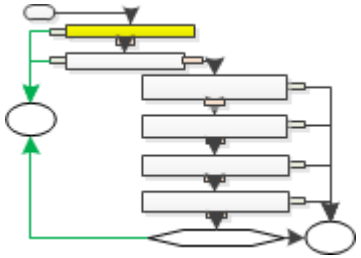
- Software modifications take many forms including, but not limited to, the following:
  - "**Adaptive** – modification of software to keep it usable in a changed or changing environment;
  - **Corrective** – reactive modification of a software product to address discovered faults; or
  - **Perfective** – modification of a software product to improve performance or maintainability".

Decision making process



Question #1

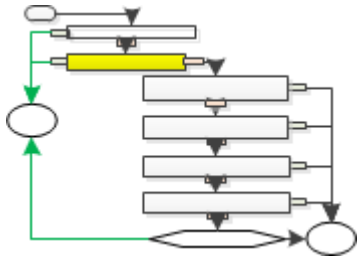
Is the change made **solely** to strengthen cybersecurity and **does not have any other impact** on the software or device?



- To answer yes:
  - No other changes to the software or architecture are included
  - The change does not have impact on the device
    - e.g. Adding encryption where it was not used before may have impact on software or device
- If the answer to this question is yes, document the change and the rationale as discussed previously.
- If the answer is no, continue to Question 2

Question #2

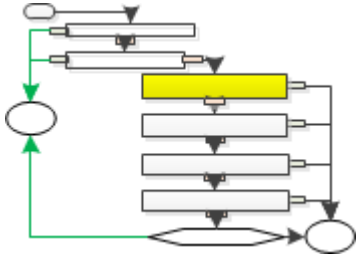
Is the change made **solely** to return the system into specification of the **most recently cleared device**?



- To answer yes:
  - Specification is for most recently cleared device
  - The change does not have an overall impact on the device that could significantly affect safety, effectiveness or intended use
- If the answer to this question is yes, document the change and the rationale as discussed previously.
- If answer is no, continue to Question 3

Question #3

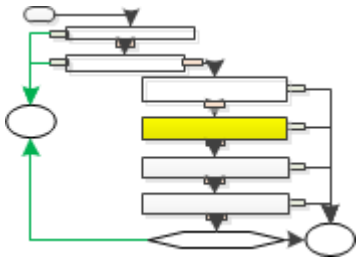
Does the change **introduce** a **new cause or modify an existing cause** of a hazardous situation that could result in significant harm and that is not effectively mitigated in the most recently cleared device?



- Criteria for assessing:
  - New Cause or modification of existing cause
  - Level of harm is serious or more severe
  - New cause or modification of existing cause is not already effectively mitigated
- If the all criteria are met, a new 510(k) is likely required.
- If answer is no, continue to Question 4

Question # 4

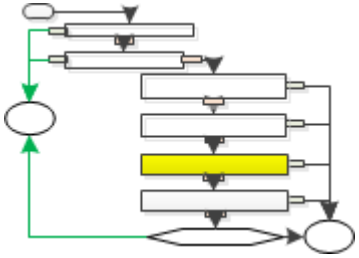
Does the change introduce a new **hazardous situation** or modify an existing hazardous situation that could result in significant harm and that is not effectively mitigated in the most recently cleared device?



- Criteria for assessing :
  - Change introduces a new hazardous situation
  - Level of harm is serious or more severe
  - New hazardous situation is not already effectively mitigated
- If the all criteria are met, a new 510(k) is likely required.
- If answer is no, continue to Question 5

Question # 5

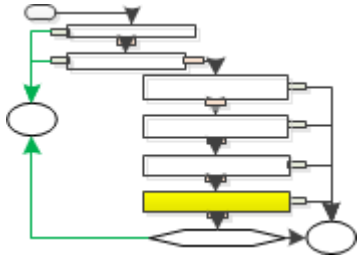
Does the change create or necessitate a new **risk control measure** or a modification of an existing risk control measure for a hazardous situation that could result in significant harm?



- Software change :
  - Is a new risk control
  - Modifies an existing risk control
  - Directly impacts an existing risk control
- Risk control prevents significant harm
- If the answer to this question is yes, a new 510k is likely required.
- If answer is no, continue to Question 6

Question # 6

Could the change significantly affect **clinical functionality** or **performance specifications** that are directly associated with the intended use of the device?



- Addition or change to clinical functionality or performance specifications
- Change is directly associated with intended use
  - If the intended use is changed, change is outside scope of this guidance.
- If the answer to this question is yes, a new 510k is likely required.
- If answer is no, continue to Additional Factors

Evaluate additional software factors that may affect the decision to file

- **"Infrastructure"** modifications made to the software support system.
- **"Architecture**" modifications to the overall structure of the software.
- **"Core algorithm"** modifications made to an algorithm that directly drive the device's intended use.

Additional Factors cont.

- **"Clarification of Requirements – No change to Functionality"** are changes made to clarify software requirements after a product has received premarket clearance.
- **"Cosmetic Changes – No change to Functionality"** are changes made to the appearance of the device that do not impact the clinical use of the device.

Additional factors cont.

- **"Reengineering or refactoring"** SW maintenance techniques.

  Reengineering - the examination and alteration of SW to reconstitute it in a new form, and includes the subsequent implementation of the new form.

  Refactoring - is a disciplined technique for restructuring a SW program's internal structure without changing its clinical performance specification, to improve a program structure and its maintainability.

Comments: Software Mods

- Most comments applied to both guidances
- Consistency with General Mods guidance
- Suggestions that Level of Concern factor into decision
  - LOC is used to determine level of documentation to provide in a submission, not whether the change could significantly affect
- Requests to add examples

Next Steps

- Comment period ended November 7, 2016
- 21st Century Cures Sec. 3059(b) requires FDA to finalize guidances by November 8, 2017
- FDA is considering comments and working to finalize as we speak

Questions ?

General questions, contact Division of Industry and Consumer Education: DICE@fda.hhs.gov

Questions about the 510(k) Device Modifications Guidances?

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