Report to Congress

Report on FDA's Policy to be Proposed Regarding Premarket Notification Requirements for Modifications to Legally Marketed Devices

U.S. Department of Health and Human Services

Food and Drug Administration

Date 1/7/14

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

Executive Summary

The Food and Drug Administration Safety and Innovation Act (FDASIA)[1] became law on July 9, 2012. FDASIA added section 510(n)(2) to the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) (21 USC 360(n)(2)). This new provision requires, no later than eighteen months after enactment of FDASIA, the Secretary of Health and Human Services to submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report on when a premarket notification under section 510(k) of the FD&C Act (or a "510(k)") should be submitted for a modification to a legally marketed 510(k) device. This report fulfills that requirement.

In developing this report, the Food and Drug Administration (FDA or the Agency) has sought the input of interested stakeholders on the Agency's 510(k) device modifications policy at several different junctures. Patient and consumer groups generally have supported greater regulatory oversight of modified 510(k) devices, including requiring manufacturers to submit periodic reports and the Agency to conduct more comprehensive premarket review of modified 510(k) devices. Major device trade associations and several companies, however, have advocated that FDA should use the current guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device" (1997) (1997 Guidance), as the foundation of its policy, with some small changes to that document to ensure clarity and consistency of interpretation. The Agency's analysis has shown that although there are certain areas of its 510(k) device modifications policy that should be updated or revised, the 1997 Guidance is a solid foundation and should remain mostly unchanged. Therefore, this report outlines the following plans for developing and issuing policy on when to submit a 510(k) for modifications to a legally marketed 510(k) device:

1. FDA intends to make targeted revisions to the 1997 Guidance to address specific issues, including clarifying key terms from FDA's regulations and explaining how quality system processes may be used in deciding whether to submit a 510(k), but the Agency intends to leave the overarching policy framework intact.

2. FDA intends to add an updated flowchart and additional appendices to the 1997 Guidance, including an appendix that contains examples of device changes that do and do not require 510(k) submissions, and an appendix that contains guidance on how companies should document their decision-making process and rationale regarding 510(k) device modification submission decisions.

3. FDA may, as appropriate, develop device-specific recommendations for types of changes that may require a new 510(k) and include those recommendations in device-specific guidances.

4. FDA intends to develop a separate guidance on 510(k) submissions for changes to device software.

[1] Public Law No. 112-144.

FDA plans to continue to seek the input of interested stakeholders as it develops an updated version of the 1997 Guidance. FDA would first publish any updated guidance as a draft, permitting further opportunity for review and comment by interested stakeholders before a final guidance is issued. FDA expects that the analyses and recommendations in this report will serve as the foundation for a revised policy on when to submit a 510(k) for modifications to a legally marketed 510(k) device. FDA intends to adopt a policy that will leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of the safety and effectiveness of modified 510(k) devices.

Table of Contents

I. Introduction 1

II. Background 1

III. Current 510(k) Device Modifications Policy 3
A. 510(k) Device Modifications Policy – Overview 3
B. 21 CFR 807.81(a)(3) 3
C. The Current Device Modifications Guidance Document – Deciding When to Submit a 510(k) for a Change to an Existing Device, January 10, 1997 4
D. Device-Specific Guidance Documents 5
E. The Special 510(k) Program 6
F. The Quality System Regulation, 21 CFR Part 820 6
G. Policy of Foreign Agencies 6

IV. External Stakeholder Input on Current 510(k) Device Modifications Policy 7
A. Development of the 510(k) Working Group Recommendations 7
B. AdvaMed Comments from 2010 8
C. MDUFA III Negotiations Outreach 9
D. Industry Feedback on 2011 Draft Guidance 9
E. June 13, 2013, Public Meeting on 510(k) Device Modifications 10
F. Industry Comments 11
G. Patient and Consumer Comments 12

V. Analysis of 510(k) Device Modification Examples 13

VI. Proposed 510(k) Modifications Policy 15
A. Interpretation of Key Terms 15
B. Processes for Industry to Determine Whether a Modified Device Needs a New 510(k) 16
C. Leverage of Quality System Requirements 18

VII. Appendices 20
Appendix I – Definitions of Important Terms and Acronyms Used in this Report 20
Appendix II –Section 604 of FDASIA 22
Appendix III – Federal Register Notice for the June 13, 2013 Public Meeting on 510(k) Device Modifications 24
Appendix IV – Inspection Documentation Examples 30
Appendix V – 1997 510(k) Device Modifications Guidance 38
Appendix VI – 2011 Draft 510(k) Device Modifications Guidance (withdrawn) 83

I. Introduction

Under section 604 of FDASIA, this report must include the following (see Appendix II for the full text of section 604):

1. The Secretary's interpretation of the following terms from 21 CFR 807.81(a)(3):
    a. "could significantly affect the safety and effectiveness of the device" – 21 CFR 807.81(a)(3)(i);
    b. "a significant change or modification in design, material, chemical composition, energy source, or manufacturing process" – 21 CFR 807.81(a)(3)(i); and
    c. "major change or modification in the intended use of the device" – 21 CFR 807.81(a)(3)(ii).

2. A discussion of possible processes for industry to use to determine whether a new 510(k) is necessary for a modified device.

3. An analysis of how the existing quality system requirements can be leveraged to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified 510(k) devices.

FDASIA also required that the input of interested stakeholders be considered in developing the report. In addition, FDASIA required withdrawal of FDA's 2011 draft guidance document on deciding when to submit a 510(k) for a modified 510(k) device; the guidance was withdrawn on July 17, 2012. (See Appendix VI for the withdrawn 2011 draft guidance.) It also mandated that FDA's 1997 guidance, entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device," remain in effect until any guidance or regulation is subsequently issued on this subject. This report will discuss (1) FDA's current regulation of modifications to legally marketed medical devices subject to premarket notifications, (2) input that the Agency has received from external stakeholders on its 510(k) device modifications policy, and (3) a policy on 510(k) device modifications that will advance FDA's mission of protecting the public health and facilitating medical device innovation.

II. Background

The mission of FDA's Center for Devices and Radiological Health (CDRH or the Center) is to protect and promote the public health by ensuring that patients and providers have timely and continued access to safe, effective, and high-quality medical devices. Not only should FDA take steps to ensure that medical devices on the market are safe and effective, but the Agency should also provide an efficient path to market for new and innovative devices so patients and providers have the best health care tools at their disposal. As part of this dual goal, FDA must have an efficient regulatory pathway for modified medical devices to reach patients and providers in a timely manner. The "modified medical devices" referred to in this report are medical devices

that have been previously cleared for market through 510(k) submissions and have been modified in some way.[2]

A large number of the 510(k) submissions that FDA receives are for modified devices. Manufacturers are constantly seeking to upgrade and improve their devices by, for example, changing materials, device sizes and shapes, and software, or by adding or removing features or device indications. Although these modifications are often successful as device improvements, there are instances where they can create significant safety and/or effectiveness problems (some of these examples are described in Section V of this report). FDA is able to identify some of these issues in premarket review of modified devices that require new 510(k) submissions, identifying cases where appropriate testing has not been done, where applicable risks have not been considered, or where results of testing are simply insufficient. FDA's 510(k) device modifications policy is geared toward identifying which device modifications may cause such issues and ensuring that there is effective regulatory oversight of these changes, without impeding the evolution of medical device science and technology.

FDA's current guidance document on 510(k) device modifications was published on January 10, 1997.[3] The Special 510(k) program was developed by FDA – through a separate guidance document[4] with input from stakeholders – to utilize newly established design control provisions of the Quality System regulation, including design verification and validation processes, and to provide manufacturers[5] a streamlined premarket review for certain device modifications that require 510(k) submissions.

In July 2011, FDA published a draft guidance document entitled "Deciding When to Submit a 510(k) For a Change to an Existing Device" (2011 Draft Guidance). The impetus for issuing that proposed update of the 1997 Guidance was: (i) to revise language to improve consistency in the application of the guidance, (ii) to account for the evolution of medical device technology in areas such as software and wireless technologies, and (iii) to provide greater clarity in light of certain failures by manufacturers to apply the 1997 Guidance as originally intended in decisions about when to submit a new 510(k).[6] FDA did not intend to fundamentally change the modifications policy described in the 1997 Guidance in that update; however, when FDA published the 2011 Draft Guidance and solicited comments, the Agency became aware of industry concerns with the draft modifications guidance. In response, the Agency extended the comment period and held multiple meetings with industry representatives and senior CDRH

[2] New devices that have not yet been marketed, devices that are subject to premarket approval (PMA), and devices that are exempt from both PMA and 510(k) premarket review are covered by separate regulations and are not within the scope of this report.

[3] See *Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)*, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

[4] See *The New 510(k) Paradigm – Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications*, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm.

[5] For the purposes of this document, the term "manufacturer" includes any company that holds a 510(k) for a cleared device, even if it does not actually fabricate the device.

[6] For example, a gynecological mesh manufacturer did not submit a 510(k) for its product after determining, under its interpretation of the 1997 Guidance, that its product was as safe and effective as a gynecological mesh device marketed by a different manufacturer. The manufacturer made such a determination despite the fact that the 1997 Guidance expressly applies only to modifications made to legally marketed devices by the *same* manufacturer of the legally marketed device.

management. Because FDASIA directed FDA to withdraw the 2011 Draft Guidance, no revisions to that draft guidance were issued. In developing this report, FDA has continued to solicit input on its policy concerning 510(k)s for modified devices.

III. Current 510(k) Device Modifications Policy

A. 510(k) Device Modifications Policy – Overview

FDA's current device modifications policy is set forth in 21 CFR 807.81(a)(3), which addresses when a manufacturer must submit a 510(k) for a device modification, and the 1997 Guidance, which explains how FDA interprets and applies section 807.81(a)(3). In addition, there are several other relevant guidance documents and regulations. For example, certain device-specific guidance documents, such as the guidance for daily wear contact lenses[7] and the guidance for pulse oximeters,[8] include recommendations for those specific device types on which types of modifications do or do not need new 510(k) submissions. Another guidance document, entitled "The New 510(k) Paradigm – Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications," describes Special 510(k)s, which are streamlined 510(k) submissions specifically designed for manufacturers making certain modifications to their previously cleared devices. Each of these documents is briefly described below.

B. 21 CFR 807.81(a)(3)

Under 21 CFR 807.81(a)(3), a 510(k) must be submitted when "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 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."

Section 604 of FDASIA requires FDA to include in this report its interpretation of the terms "could significantly affect safety or effectiveness of the device," "a significant change or modification in design material, chemical composition, energy source, or manufacturing process," and "major change or modification in the intended use of the device." FDA believes that these terms provide the Agency with necessary flexibility regarding when 510(k)s are required for modified devices.

---

[7] See *Premarket Notification [510(k)] Guidance Document for Class II Daily Wear Contact Lenses*, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080928.htm.

[8] See *Pulse Oximeters – Premarket Notification Submissions [510(k)s]*, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm341718.htm.

21 CFR 807.81(a)(3) may be applied to many different types of devices with different intended uses, different designs, different levels of complexity, and different levels of risk. A change that could significantly affect the safety of one device and trigger the need for a 510(k) submission may not significantly affect the safety of another device. For instance, a change to the materials used in a knee implant may significantly change the device's strength and toxicity profile, and FDA would want to review such a change to a 510(k) submission; however, a change in the materials used in a cardiac monitor that displays a patient's heart rate without ever touching that patient is unlikely to significantly affect the safety or effectiveness of the device, so FDA would not need to review a 510(k) for that device change. The qualifying terms "significant" and "major" in this regulation allow for that flexibility, so industry can make design changes without having to submit unnecessary 510(k)s for the many small changes that manufacturers make to devices every day.

There are limits to how flexible these terms are, however, and the Agency believes that the 1997 Guidance could more clearly describe the limits of the terms in section 807.81(a)(3) and clarify what the Agency views as a change that "could significantly affect" safety or effectiveness and a "major change or modification" in intended use. For instance, FDA has heard that manufacturers sometimes believe that any change that constitutes an improvement to a device would not require a new 510(k). Device modifications, however, are almost always intended as improvements. Even modifications that are made to cut manufacturing costs are rarely, if ever, intended to decrease the device's safety or effectiveness. All changes, regardless of the manufacturer's reason for making them, need to be assessed according to the regulation – *could they significantly affect the safety or effectiveness of the device*, or are they *a major change or modification in intended use*? FDA has also observed that manufacturers sometimes rely on testing to demonstrate that a change or modification to a medical device *does not* affect safety or effectiveness, as opposed to showing whether it *could* affect device safety or effectiveness. Each of these misinterpretations of the regulatory language could lead to modified medical devices being marketed without appropriate FDA oversight (Examples of such modifications are discussed in Section V). For these reasons, the Agency believes that future guidance should more clearly explain the language of 21 CFR 807.81(a)(3).

C. The Current Device Modifications Guidance Document – Deciding When to Submit a 510(k) for a Change to an Existing Device (January 10, 1997)

The 1997 Guidance does not attempt to set out hard-and-fast rules for when a change triggers the requirement of a new 510(k) submission, but instead lays out a process for determining when any given device modification meets the regulatory criteria in section 807.81(a)(3) and requires a new 510(k). That guidance acknowledges the challenges of balancing the need for both flexibility and clarity in developing policy concerning 510(k) modifications. It describes the challenge of defining broad, amorphous principles of general applicability ("the variety of device types currently marketed, as well as the myriad changes that occur as technology evolves, are so diverse that one or two unifying principles cannot possibly account for all possible situations") -- and the challenge of enumerating all device types and all potential types of changes ("the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely

to keep pace with an ever-changing technology").[9] By design, the 1997 Guidance steers a middle course:

> "Between the two extremes of broad principles and detailed enumeration is the area where models can be developed to assist in the decision-making. If created and used properly, such a model could provide guidance leading toward a rational answer as to whether a 510(k) is necessary in the large majority of circumstances. This document proposes a flowchart model that can be used by manufacturers in their decision-making to analyze how changes in devices may affect safety or effectiveness. In the model, we attempt to address changes to devices at a level detailed enough so that application of the broad principles contained in the regulations would minimize disagreements between manufacturers and the Agency. The goal of the model is to provide guidance in answering a manufacturer's questions on whether a 510(k) should be submitted for a particular type of change and to minimize the number of instances where the answer would be uncertain. Taken as a whole, this guidance, and the model it describes, provides the agency's best definition of when a change to a device could significantly affect safety and effectiveness."[10]

Rather than provide concrete definitions of terms used in section 807.81(a)(3), the 1997 Guidance presents a logical scheme for how one might assess a device modification by answering a series of questions, including "does the change affect the indications for use?" or "are clinical data necessary to evaluate safety and effectiveness for purposes of determining substantial equivalence?" The questions are represented visually in flowcharts at the end of the document. Answering each question leads one through the flowcharts until one arrives at one of two conclusions – either a new 510(k) is necessary, or a 510(k) is not necessary and the change should simply be documented in the manufacturer's files.

D. Device-Specific Guidance Documents

FDA has published device-specific guidance documents for many 510(k) products.[11] The purpose of these documents is to provide recommendations for a particular type of device so that manufacturers intending to market that type of device have transparency into the Agency's thinking on how the manufacturer should demonstrate substantial equivalence or fulfill other regulatory expectations. Some device-specific guidances discuss potential device modifications for the device and the criteria that FDA considers in determining whether, under 21 CFR 807.81, a new 510(k) would be necessary for device modifications within that device type. For instance, the guidance for daily wear contact lenses states that modifications involving surface treatments (for example, those "reducing protein deposit or improving wettability") would require new 510(k)s under 21 CFR 807.81, whereas certain labeling changes would not require 510(k)s under the regulation. Moreover, as it acknowledged, the 1997 Guidance was not intended to supplant

[9] 1997 Guidance at pp. 1, 2.
[10] 1997 Guidance at p. 2.
[11] FDA's guidance documents can be found in a database at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

device-specific guidances, but rather aimed to address areas not otherwise addressed in device-specific guidances.

E. The Special 510(k) Program

For the benefit of industry and FDA review staff, the Agency created the Special 510(k) program in 1998 to provide a streamlined premarket submission process for certain device modifications. If a manufacturer modifies its device and does not change the indications for use or the fundamental scientific technology of the device, it is eligible to submit a Special 510(k). These 510(k)s are reviewed in 30-day cycles, one-third the typical 90-day review period for 510(k)s.

Special 510(k)s also do not need to include as much performance information as traditional 510(k) submissions. Special 510(k)s simply need to describe the device modification that prompted the 510(k) submission, identify the risk analysis method(s) used to assess the impact of the modification as well as the results of the analysis, identify the verification and/or validation activities required, and provide a declaration of conformity with design controls.

This focused review program leverages quality system information to decrease the premarket burden on manufacturers; instead of submitting a traditional 510(k) with a longer review timeframe, manufacturers provide FDA with certain quality system information and certify that the data behind the summarized information submitted as part of a Special 510(k) is documented in company records and available for Agency review during a postmarket inspection.

F. The Quality System Regulation, 21 CFR Part 820

The Quality System regulation outlines the basic elements of a system for designing and producing a medical device that meets appropriate design specifications. This covers many aspects of designing and producing a medical device, but the requirements most relevant to device modifications are laid out in section 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."

Elements of section 820.30(i) are discussed in the 1997 Guidance and will be discussed further in this report, namely, recommendations for documentation of design changes when the manufacturer decides it is not necessary to submit a new 510(k), and the role of verification and validation in the decision to submit a new 510(k). It is important to note that quality system information as required by the Quality System regulation is rarely part of the premarket assessment for 510(k)s and is typically assessed only during postmarket inspections.[12]

[12] Section 513(f)(5) of the FD&C Act (21 USC 360c(f)(5)) allows FDA to withhold initial classification of a device for findings related to quality system requirements if "there is a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health."

G. Policy of Foreign Agencies

Foreign regulatory bodies, such as Health Canada (HC), have adopted a variety of regulations and guidance documents regarding medical device modifications. FDA's regulation of modifications is generally similar to that of HC and HC's guidance document on medical device modifications is very similar to FDA's 1997 Guidance.[13] HC has regulatory requirements similar to FDA – "significant changes" require amended marketing licenses, and HC's guidance explains which modifications qualify as "significant changes."[14]

The European Union (EU), however, has a very different regulatory system. One major difference is that under the EU system, notified bodies frequently review quality system information prior to the marketing of most medical devices.[15] As noted above, FDA typically does not conduct premarket review of quality system information for 510(k) devices and does not have the authority, in most circumstances, to withhold a device's clearance based on quality system deficiencies.[16] For this reason, FDA generally cannot use quality system information in the same manner that such information is used in the EU.

IV. External Stakeholder Input on Current 510(k) Device Modifications Policy

FDA has solicited input on its 510(k) device modifications policy from interested stakeholders through several forums. In August 2010, the Agency's 510(k) Working Group made several recommendations on the 510(k) program in general, including specific recommendations related to the 510(k) device modifications policy. Those recommendations were based, in part, on comments from the industry trade group AdvaMed, which were received earlier in 2010. This led to the creation of a 510(k) Plan of Action for implementation of these recommendations, which included issuing an updated 510(k) Modifications Guidance (the 2011 Draft Guidance).

FDA discussed the 2011 Draft Guidance with industry representatives during negotiations for the Medical Device User Fee Amendments of 2012 (MDUFA III), received many comments from industry on the 2011 Draft Guidance in a publicly-accessible docket, and held an all-day public meeting on June 13, 2013, with a panel that included representatives from patient and consumer groups, foreign regulators, and industry to discuss FDA's 510(k) device modifications policy. FDA agreed to several requests for meetings from industry groups prior to the June 2013 public meeting, and the Agency has agreed to additional such meetings since then. A summary description of the feedback received from each of these forums is provided below.

---

[13] See HC's "Guidance for the Interpretation of Significant Change of a Medical Device," available at http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/md-im/applic-demande/guide-ld/signchng_modimportante-eng.pdf.

[14] See section 34 of the Medical Device Regulations (SOR/98-282), available at http://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/page-7.html#h-17.

[15] See Medical Device Directive 93/42/EEC, Article 11, Conformity Assessment Procedures, available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:en:HTML.

[16] See section 513(f)(5) of the FD&C Act (21 USC 360c(f)(5)).

A. Development of the 510(k) Working Group Recommendations

In September 2009, FDA convened a 510(k) Working Group tasked with evaluating the 510(k) program and exploring actions that CDRH could take to strengthen the program and improve the consistency of 510(k) decision making. A subgroup of the 510(k) Working Group focused specifically on device modifications.

To gather input from FDA's external constituencies, the 510(k) Working Group held a public meeting on February 18, 2010, entitled "Strengthening the Center for Devices and Radiological Health's 510(k) Review Process."[17] The group collected written comments through a public docket that was open from January 27, 2010 through March 19, 2010.[18] Although device modifications policy was not the primary focus of the plan or the meeting, concerns related to device modifications were raised by both FDA and external stakeholders during the February 18, 2010 public meeting and in comments submitted to the public docket. FDA expressed concern that modifications to 510(k) devices are often not submitted for premarket review when they should be submitted. Recommendations from external stakeholders regarding device modifications included suggestions to revise the 1997 Guidance to clarify and update certain points.

In August 2010, based on input from internal CDRH discussions, the February 18, 2010 public meeting, and comments provided to the public docket, FDA published the preliminary report and recommendations of the 510(k) Working Group.[19] Regarding 510(k) device modifications, the 510(k) Working Group recommended the following:

(1) CDRH should revise the existing guidance to clarify what types of modifications do or do not warrant submission of a new 510(k), and, for those modifications that do warrant a new 510(k), what modifications are eligible for a Special 510(k).

(2) CDRH should explore the feasibility of requiring each manufacturer to provide regular, periodic updates to the Center listing any modifications made to its device without the submission of a new 510(k) and clearly explaining why each modification noted did not warrant a new 510(k).

B. AdvaMed Comments from 2010

AdvaMed provided a letter to FDA on May 21, 2010, in which it provided an assessment of the 1997 Guidance. In that letter, AdvaMed indicated that the guidance had served industry well since 1997 and stated its strong support for FDA's effort to update the guidance so that it would continue to be a useful tool for industry and FDA. AdvaMed provided an analysis of the areas in

[17] Meeting materials, including a video recording and transcript, available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm193327.htm.
[18] FDA-2010-N-0054.
[19] Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220784.pdf.

the existing guidance that it believed were vague, confusing, or not consistently implemented across industry. Based in part on these concerns, the Agency attempted to provide greater clarity in the 2011 Draft Guidance.

C. *MDUFA III Negotiations Outreach*

Additional outreach to industry included discussions at the MDUFA III negotiation meetings which were attended by FDA and representatives of the device industry. At such a meeting on August 9, 2011,[20] a presentation was made discussing the concepts in the 2011 Draft Guidance. FDA indicated during that meeting that the document had been published in draft form and that the Agency was open to suggestions for new wording, additional examples, and any other means of improving the document.

D. *Industry Feedback on 2011 Draft Guidance*

In response to the comments (discussed above) calling for some improvements to the 1997 Guidance, FDA published the 2011 Draft Guidance on July 27, 2011. FDA did not intend to fundamentally change the policy described in the 1997 Guidance, but rather intended to address the language in that document that some manufacturers had asserted was unclear and had led to inconsistent interpretations of when a 510(k) is necessary for a device modification. All comments received during the comment period for the 2011 Draft Guidance were from device manufacturers and industry groups, many of whom expressed concern that the draft constituted a departure from past policy and would result in more burdensome premarket requirements.[21]

Some questioned whether a new guidance was necessary at all, and many suggested that although changes to the 1997 Guidance might be helpful, the revisions proposed in the 2011 Draft Guidance were more extensive than necessary and would result in increased premarket burden for modified devices. Numerous commenters suggested that the Draft Guidance be revised by attaching a flowchart that relied more on quality system requirements – primarily design verification and validation – and integrated risk management principles. In addition, FDA held multiple meetings with industry representatives to discuss the 2011 Draft Guidance and possible policy revisions, including the use of critical specifications, risk-based stratification, and periodic reporting, suggestions that were later used to develop discussion topics for the 2013 public meeting held on 510(k) device modifications.

FDA believed that these conversations were constructive and expected that they would result in significant changes being made to the final document. However, FDASIA mandated that the Draft 2011 Guidance be withdrawn and that the 1997 Guidance remain in effect until after the

[20] Minutes of that meeting are available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm272699.htm.

[21] Comments available at www.regulations.gov under docket number FDA-2011-D-0453.

submission of this report to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate.

E. June 13, 2013, Public Meeting on 510(k) Device Modifications

FDA held an all-day public meeting regarding the 510(k) device modifications policy on June 13, 2013, at Agency's White Oak, Maryland campus.[22] The meeting was announced as an opportunity for external stakeholders and the Agency to come together to discuss FDA's past, present, and future policy on 510(k) device modifications. More than 300 people registered to attend in person, and another 900 people registered to attend via webcast. Topics of discussion, which were posted on the meeting website and described more fully in the *Federal Register* meeting announcement[23] (available as Appendix III), included:

1. Potential use of risk management in 510(k) device modifications decisions – FDA sought proposals on how to incorporate risk management into its policy to ensure appropriate and consistent decisions by industry and FDA staff.

2. Potential reliance on design control activities – FDA sought proposals for how industry and FDA could utilize design control activities, such as design verification and validation, to ensure that device modifications are appropriately evaluated prior to marketing.

3. Potential use of critical specifications – FDA sought proposals on whether it could incorporate the use of critical specifications in determining whether device modifications require new 510(k) submissions in a manner that would ensure appropriate and consistent decisions by industry and FDA staff.

4. Potential risk-based stratification of medical devices – FDA sought input on the practicality of stratifying devices requiring 510(k)s by risk, where lower risk devices would not require 510(k)s for most modifications, if those modifications were included in periodic reports submitted to the Agency.

5. Potential periodic reporting – FDA sought comments on the possibility of subjecting legally-marketed 510(k) devices to periodic reporting requirements.

6. Potential other solutions – FDA sought comments on combinations of the above or other options above, and on other options not mentioned here.

Each topic was based on suggestions arising from interactions with or comments from external stakeholders. Interested stakeholders made presentations on all proposed topics through the first half of the day, and in the second half of the day, all participants were invited to join an

[22] Meeting materials, including webcast recording and presentation materials, available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm347888.htm.
[23] 78 FR 26786.

interactive panel discussion. The panel consisted of members of industry, consumers, patient representatives, foreign regulators, and FDA staff. Most of the panel discussion centered on industry's frequently suggested use of risk management and reliance on design control activities. Although FDA's current device modifications policy already utilizes these tools, industry consensus was that FDA should rely upon them more heavily.

Subsequent conversations and meetings with industry representatives have been productive in determining how these tools might be further employed as part of the Agency's general device modifications policy. Although originally proposed by industry, use of critical specifications and risk-based stratification were generally met with skepticism by industry both during the meeting and in subsequent comments to the public docket for the meeting. Patient and consumer groups, on the other hand, generally recommended further restrictions on industry's ability to market modified devices without FDA premarket review. They supported periodic reporting of device modifications, but did not support the other discussed measures if they resulted in less premarket oversight of modified devices. These comments demonstrate the varying opinions on proper regulatory oversight of medical device modifications and the need to assure patients and consumers that FDA is exercising effective regulatory oversight of the safety and effectiveness of medical devices.

F. Industry Comments

Aside from further reliance on risk management and design control activities, the most consistent feedback that FDA received from industry was that the 1997 Guidance is very useful and should be maintained as the foundation of any new policy, albeit with some possible revisions. The industry trade organizations' comments to the meeting docket, quoted below, reflect this sentiment.

> **AdvaMed**: "The current guidance … is a well-founded document that provides a pragmatic approach to determining when a modification requires a new submission. The hallmark of a good document is its ability to withstand the test of time. We believe that the Existing Guidance has done that. It has provided a decision-making model that is flexible enough to adapt to the plethora of different device types cleared under the 510(k) program and the myriad of changes that occur as technology and scientific knowledge evolve. It recognizes that enumerating all device types and potential types of changes is impossible, and puts the onus on the manufacturer to answer key questions that determine whether a change could significantly affect safety or effectiveness, and therefore require submission of a 510(k). … With that in mind, AdvaMed recommends that FDA maintain the Existing Guidance as the foundational document, and make improvements as we describe herein."[24]
>
> **The 510(k) Coalition**: "At the June 13th meeting, different stakeholders offered different perspectives on what changes, if any, are needed to the current modifications guidance (K97-1). Some espoused the view that the core approach in the current guidance is the most

[24] AdvaMed's full comments are available at www.regulations.gov under comment ID FDA-2013-N-0430-0029.

appropriate and what is needed is simply some updating and attention to specific issues or technologies (*e.g.*, software). The Coalition is generally in this camp. Unless FDA identifies some pressing need, the Coalition's core view is that K97-1 should continue to be the basis for when a modification triggers the need to submit a new 510(k). The Coalition supports some updating of K97-1 (*e.g.*, current references, elimination of the transitional QSR discussion as that is no longer relevant, and more explicit reference to existing guidance and regulation)."[25]

The Medical Device Manufacturers' Association (MDMA): "MDMA believes that the initial guidance, published in 1997 (the '1997 Guidance'), continues to afford both the Agency and manufacturers a strong foundation for determining when a manufacturer should submit a premarket notification for a modification or change to a legally marketed device. MDMA therefore encourages the Agency to continue its reliance on the 1997 Guidance, and recommends that it be updated to more specifically incorporate Quality System Regulation testing and procedure requirements as discussed below."[26]

These statements from three major medical device trade organizations are generally in agreement with each other and with other companies that commented. Although each organization's comments differ somewhat in the extent of the changes they recommend to the 1997 Guidance, the overwhelming consensus is to retain the foundation of that document as the basis for FDA's 510(k) device modifications policy.

G. Patient and Consumer Comments

Consumer and patient representative views differed substantially from those of industry. The Patient, Consumer, and Public Health Coalition stated that the 1997 Guidance gives manufacturers too much flexibility in deciding when modifications affect the safety and effectiveness of a device. The Coalition did not support further reliance on design control activities, or use of critical specifications or risk-based stratification where certain groups of devices might be exempt from submitting 510(k)s for device modifications. The group did support the use of periodic reporting and risk management, with specific guidelines.[27] The National Women's Health Network expressed similar concerns; the group did not support further use of design controls, critical specifications, or risk-based stratification. The National Women's Health Network believed that risk management is a useful tool given specific guidelines, and it supported periodic reporting.[28]

Other consumer and patient group comments were similar, and included concerns about manufacturers deciding when to submit modified devices for premarket review. One comment

[25] The 510(k) Coalition's full comments are available at www.regulations.gov under comment ID FDA-2013-N-0430-0028.
[26] MDMA's full comments are available at www.regulations.gov under comment ID FDA-2013-N-0430-0032.
[27] The Patient, Consumer, and Public Health Coalition's full comments are available at www.regulations.gov under comment ID FDA-2013-N-0430-0034.
[28] The National Women's Health Network's full comments are available at www.regulations.gov under comment ID FDA-2013-N-0430-0009.

proposed that FDA require 510(k)s for all device modifications,[29] and another comment, from an anonymous third-party regulatory consultant for medical devices, alleged that companies abuse the 510(k) device modifications policy and included examples of instances where device companies did not submit 510(k)s for devices that they knew required submissions.[30]

V. Analysis of 510(k) Device Modification Examples

FDA utilized multiple sources of information to identify examples of decisions regarding device changes made by industry using the recommendations outlined in the 1997 Guidance. From analyzing these examples, the Agency was able to draw some conclusions regarding the strengths and weaknesses of the 1997 Guidance.

One source of examples was inspection reports, where investigators, during routine inspections, collect information regarding a manufacturer's change process, as well as reports of all recent changes. From these examples, we were able to determine that the most common misuse of the 1997 Guidance involved using the flowchart at the end of the document alone, without the text of the guidance, when deciding whether to submit a new 510(k). In many cases, a notated version of the flowchart was also the only piece of decision-making documentation kept in company records, without any explanation of how the manufacturer followed the flowchart. Examples of this are shown in Appendix IV. In one example, a manufacturer photocopied the flowchart and circled decision points leading to the conclusion that a 510(k) was not required; in another, a manufacturer reproduced part of the flowchart, excluding most of the decision points. None of the decisions made in these examples was explained. In some cases, the documentation does not even describe the device modification being evaluated. FDA deems this method of assessment and documentation to be inadequate. The text and concepts from the 1997 Guidance are meant to be used in conjunction with the flowcharts, and some manufacturers do not consider concepts in the text of the guidance, limiting the decision to the narrow context of the flowchart alone. Even if the decision was ultimately correct, often no documentation of the thought process underlying it exists, thus making it difficult for anyone, either internal or external to the company, to understand the rationale for the submission or lack of submission of a 510(k). After reviewing inspection reports, FDA found inadequate and incomplete documentation to be pervasive. Adding information on appropriate documentation to future FDA guidance on 510(k) device modifications may ensure better documentation and possibly more thorough decision-making.

In addition to documentation problems, FDA has identified examples of device modifications that demonstrate what the Agency sees as some shortcomings in the 1997 modifications guidance. For example, when a manufacturer increased the size of a spinal implant, it evaluated the mechanical performance but did not account for any other risks. The ease of surgically placing a larger implant and changes in the effectiveness of the larger implant, for example, were not considered. FDA believes it could better emphasize for industry the need to consider such

[29] Full comments available at www.regulations.gov under comment ID FDA-2013-N-0430-0008.
[30] Full comments available at www.regulations.gov under comment ID FDA-2013-N-0430-0007.

impacts to enable industry to better understand the need to perform a full risk analysis in order to determine whether a modification could raise new issues.

Changes in materials are a particularly difficult issue for 510(k) modification submission decisions. This type of change can affect not only the biocompatibility of a device, but also its design and end performance. Some of the most difficult issues with changes in materials revolve around materials suppliers, who are constantly changing the products they offer, often without any warning to manufacturers, and then replacing materials used in their devices. These situations are further complicated because suppliers are not always willing to divulge the formulation of their materials to manufacturers. FDA's analysis found that manufacturers are sometimes unclear on how to proceed in these instances. Any future modifications guidance should address this clearly.

In some cases, FDA has identified actual device changes that could – and do, in fact – significantly affect safety and effectiveness, but were not reported in new 510(k)s. While the Agency is aware of only a small percentage of changes that were *not* reported in a 510(k), which it generally learns of through postmarket inspection, FDA's assessment of changes that it has reviewed indicates that manufacturers have misinterpreted or misapplied certain aspects of the 1997 Guidance. Although FDA's analysis has also found device changes that are adequately assessed, documented, and carried through to production, the following examples show that some manufacturers are not submitting 510(k)s for certain modifications that require new submissions under 21 CFR 807.81(a)(3), which could put patients at risk. The Agency believes that although the 1997 Guidance is generally effective, these examples demonstrate that additional clarity would help to ensure the safety and effectiveness of modified devices.

> **Annuloplasty ring –** An annuloplasty ring for correction of mitral valvular insufficiency was modified from previously cleared devices. The modified device combined the ring material from one cleared device with the design geometry of another cleared device. At the time, the company decided that the combination of these characteristics into a new modified device did not require a new 510(k) because the device material and design geometry were each based on cleared devices. However, material and geometry are both critical features of annuloplasty rings, and an incorrect combination of the two could lead to unsafe and ineffective rings, possibly leading to significant patient health issues and the need for an open-heart surgery to replace the device. Following subsequent discussions with FDA, the company reevaluated its decision and submitted a 510(k). This example illustrates the confusion that some manufacturers have with the use of multiple cleared devices in 510(k) device modification decisions. In addition, FDA's review of the device found that additional validation testing was necessary to demonstrate that the device performed as intended.
>
> **Troponin Assay** – A company made several changes to its troponin assay over several years. It determined that none of the changes required a new 510(k). However, FDA identified a trend in adverse events for this device, and began talking with the company. During those discussions, the modifications made to the system came to light, as well as a performance change in the test. The company had not considered the modifications to be

significant. After review, FDA informed the company that several of the modifications were required to have clearance of a new 510(k) because they could significantly affect the safety and effectiveness of the device by potentially resulting in false negatives that could lead to delay of treatment (causing serious injury or death) or false positives that could lead to unnecessary catheterization or inappropriate treatment.

Device Sterilizer System – FDA cleared the components of a system for sterilizing devices such as endoscopes and their accessories, and microsurgical and dental instruments. FDA evaluated multiple changes made by the manufacturer to the device without the submission of a new 510(k), including changes to the chemical composition of the sterilant, software changes, and changes in materials. FDA found that many of these changes were required to have been submitted in a new 510(k), and in particular, that some of the changes could and did affect the sterile fluid pathway of the device. Non-sterility of this device could lead to the presence of waterborne pathogens on endoscopes and other critical and semi-critical devices, which could lead to patient infections. FDA believes that additional clarity in the 1997 Guidance could help manufacturers to better understand which of these types of changes require a 510(k) submission.

VI. Proposed 510(k) Modifications Policy

To develop this report, FDA solicited input on its 510(k) modifications policy from interested stakeholders in industry, consumer representative groups, patient representative groups, and the general public, held a day-long public meeting to discuss initial feedback on its device modification policy, and held several additional meetings with industry to discuss further feedback. The Agency believes that these outreach efforts and conversations have led to a path forward that will ensure effective regulatory oversight of modifications made to 510(k) devices without being overly burdensome or impeding the evolution and improvement of such devices. This concluding section will outline a 510(k) device modifications policy that FDA intends to propose in draft guidance, the details of which will be developed with further collaboration with interested stakeholders.

A. Interpretation of Key Terms

The foundation of this policy lies in FDA's interpretation of several key phrases in 21 CFR 807.81(a)(3). Specifically, Congress directed FDA, in preparing this report, to include interpretations of the following terms:

- "could significantly affect the safety or effectiveness of the device";
- "a significant change or modification in design, material, chemical composition, energy source, or manufacturing process"; and
- "major change or modification in the intended use of the device."

These terms provide the Agency with flexibility and allow FDA to account for the wide diversity of devices and to utilize device-specific, risk-based decision making. Health Canada (HC) uses very similar language in its regulation on device modifications, stating that a new premarket

submission is required for a "significant change," further defined as "a change that could reasonably be expected to affect the safety or effectiveness of a medical device."[31] During the June 13, 2013, public meeting on device modifications, Dr. Ian Aldous, Senior Evaluator at HC, stated that "there's actually some benefits to having a definition of 'significant change' that is in fact open to some interpretation. It doesn't paint you into a corner, for lack of a better phrase. It does allow a little bit of gray area there to handle situations, which, quite frankly, we just haven't thought of or might be coming down the pipe in the future, while still giving us some guidance and clarity on what the overall spirit is to identify what is not a significant change."[32]

In keeping with the flexible language of the regulation, the 1997 Guidance, rather than providing definitions of key regulatory terms, provides illustrations of how these terms apply to changes in labeling, technology, engineering, performance, and materials. FDA believes that the approach of the 1997 Guidance provides clarity concerning these terms without sacrificing flexibility, and FDA intends to retain this approach in any future guidance. Indeed, written comments to the Agency, opinions expressed at the June 2013 public meeting on device modifications, and viewpoints expressed at earlier and subsequent meetings with industry have been generally supportive of the 1997 Guidance document and the policy and decision-making process described therein, with some groups asking whether it is necessary to change the status quo and revise the current guidance at all. As quoted in Section IV, AdvaMed called the 1997 Guidance "a well-founded document that provides a pragmatic approach to determining when a modification requires a new submission" and stated that the guidance has proved its worth by "its ability to withstand the test of time." The Agency believes that the illustrative model of the 1997 Guidance, with some added clarity, will be an effective way to explain application of the terms "could significantly affect safety or effectiveness," "a significant change or modification in design material, chemical composition, energy source or manufacturing process," and "major change or modification in the intended use." The Agency plans to provide additional clarity throughout the model, and to seek input from interested stakeholders on ways to increase the clarity on the bounds of these terms and which device modifications fit within them.

B. Processes for Industry to Determine Whether a Modified Device Needs a New 510(k)

FDA's current 510(k) device modifications policy centers on providing industry with guidance on how to determine whether a modified medical device needs a new 510(k) prior to being marketed. Congress directed FDA to discuss in this report possible processes for industry to use to determine whether a new 510(k) is necessary for a modified device. As noted above, many groups, including AdvaMed, have noted issues with the 1997 Guidance. For example, these groups have said that it is vague or unclear in certain sections, that some of the decision-making points can lead to conflicting interpretations, and that the flowcharts at the end of the guidance are not entirely consistent with the language in the body of the document. FDA believes certain areas could be improved, and is aware of examples where companies using this guidance

[31] Section 34 of the Medical Device Regulations (SOR/98-282), available at http://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/page-7.html#h-17.

[32] Stated at approximately 22 minutes into part 4 of the June 13, 2013 Public Workshop Webcast: https://collaboration.fda.gov/p8zms5r6gwg/.

document did not arrive at correct determinations regarding whether their proposed device changes require 510(k)s. As described in Section V, some manufacturers fail to understand certain decision points or may misapply the flowchart to their decision-making process. Some manufacturer may reach supportable decisions on whether to submit a new 510(k), but may struggle to document the rationale for their decisions, in part because the 1997 Guidance does not address how to document these decisions.

Accordingly, FDA believes that the best plan of action for future device modifications policy is to maintain the policy as described in the current 1997 Guidance, but with targeted revisions aimed at addressing the following specific issues:

- Clarifying key terms – The Agency believes that it can provide additional clarity throughout the document by illustrating the meaning of the key terms in section 807.81(a)(3).
- Design verification and validation – Design verification and validation activities are an essential part of a company's quality system program, and, in appropriate instances, can be leveraged to reduce premarket burden. They are, however, at times misapplied in 510(k) device modification decisions. As noted in the 1997 Guidance, companies should assess whether a device modification could significantly affect safety or effectiveness, and should use testing results to confirm or refute whether that assessment is correct or needs to be reevaluated. However, this principle may be under-emphasized in the 1997 Guidance; FDA intends to revise the guidance to underscore this point.
- Changes of materials – Changes of materials are a challenging modification type. FDA intends to update the 1997 Guidance to include practical considerations on this issue, such as how to assess changes when a manufacturer's material supplier changes the formulation of the material it provides to the manufacturer, but in the interest of protecting trade secret information, the supplier refuses to disclose the exact formulation of that material.
- Technological and regulatory advancements – Medical technology has advanced greatly since the 1997 Guidance was published, and FDA regulations and policies have been updated to adapt to the changing landscape in medical devices. FDA's modifications policy – whether in the general modifications guidance or in additional stand-alone guidance documents – should be updated as well to ensure that manufacturers have up-to-date guidance on technologies such as software and wireless devices.
- Clarity of the modifications guidance document text and congruence of the text with flowcharts – The flowcharts at the end of the 1997 Guidance can be difficult to apply independently of the text in the body of the guidance, and the guidance document text would benefit from additional clarity in certain areas.

In addition to making select revisions to the current 1997 Guidance to target certain areas, FDA plans to add two new appendices to the guidance: one to provide additional examples of device changes that likely would and would not require new 510(k) submissions, and another to provide guidance on how to appropriately document the process of deciding whether to submit a 510(k)

for a device modification. Industry has stated that additional examples would be helpful in understanding FDA's device modifications policy and has requested examples of changes that would not need a 510(k) as well as those that would need one. Such an appendix is included in HC's device modifications guidance. FDA plans on using some of the examples from HC's guidance, in addition to examples the Agency has received from industry, for inclusion in a future modifications guidance and applicable examples that have been included in previous FDA guidances. FDA also plans on adding explanations of how to walk through some examples to explain the process of deciding whether a new 510(k) is necessary.

Finally, FDA plans to add an appendix on how to completely document the decision whether to submit a 510(k). This should be helpful in alleviating the issues with documentation described in Section V. FDA believes that an appendix describing how to document the decision-making process for device modifications might simplify the process for industry and provide manufacturers with a consistent approach to documenting the decision-making process and ensuring compliance with section 807.81(a)(3). Appropriate and consistent documentation will also streamline inspections of this information, which may make that process more efficient. Appropriate documentation may also improve compliance with Quality System regulation documentation requirements for design changes in situations where the modification decision was made correctly.

FDA also may expand inclusion of device-specific modifications sections in device-specific guidance documents where appropriate. A small number of guidance documents already include examples of device modifications that do and do not require a new 510(k) submission. It should be noted that any new guidance documents will be issued in draft form for public comment, to provide industry and other stakeholders the opportunity to comment on any specific examples included therein.

C. Leverage of Quality System Requirements

Congress directed FDA to analyze how existing quality system requirements can be leveraged to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices. Current 510(k) device modifications policy relies on quality system requirements in two ways: (1) to ensure safety and effectiveness of modified medical devices that do not require 510(k) submissions; and (2) to reduce premarket burden on manufacturers who do need to submit new 510(k)s and meet the requirements of the Special 510(k) program.

Regulatory oversight for device changes that are not required to be submitted in new 510(k) submissions is conducted through quality system requirements. FDA uses these requirements to ensure that there is appropriate documentation of modifications and explanation as to how device safety and effectiveness have been ensured. In developing additional guidance, FDA proposes to identify specific examples of device changes, through general and device-specific guidances, that do not require new 510(k)s but can be appropriately regulated through the quality system requirements.

As discussed in Section III, FDA also offers the Special 510(k) program, which relies on quality system information to decrease premarket burden on those manufacturers who do need to submit new 510(k)s for certain modified devices. FDA plans to continue this program.

In addition to these uses of the quality system requirements, FDA plans to discuss with interested stakeholders additional uses of the quality system. FDA believes that there may be other ways to use this information to reduce premarket burden on manufacturers who must submit new 510(k)s for modified devices. Some possible options were discussed during the June 13, 2013, public meeting (see Section IV), and FDA will continue to consider other alternatives. FDA believes that these proposals will allow the Agency to effectively oversee device modifications, but also allow industry the freedom to make modifications to currently, legally marketed devices as necessary without undue burden.

In conclusion, FDA intends to update the 1997 Guidance to provide greater clarity on when a new 510(k) is required for changes to a cleared device and processes for manufacturers to determine whether a change requires 510(k) review. FDA also intends to address in the revisions how to leverage existing quality system requirements and how to document decisions regarding changes to cleared devices. FDA welcomes comments and questions from Congress.

VII. Appendices

Appendix I – Definitions of Important Terms and Acronyms Used in this Report

510(k): A premarket review submission, also known as a premarket notification, in which manufacturers alert FDA that they plan to market a medical device in the United States, which FDA must clear prior to marketing. A device can be cleared for market if the 510(k) submission demonstrates that the device is substantially equivalent to a legally marketed device (a predicate device) (see *predicate device and substantial equivalence* definitions below). 510(k) submissions are required for most class II medical devices, and some class I and class III devices.

CDRH: Center for Devices and Radiological Health

EU: European Union

FDA: Food and Drug Administration

FDASIA: The Food and Drug Administration Safety and Innovation Act

HC: Health Canada, the medical device regulatory agency of Canada

Intended Use: Intended use refers to "the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article ...."[33]

Indications for Use: An indication for use is "[a] general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."[34] The indications include all the labeled patient uses of the device, for example:

- the condition(s) or disease(s) to be screened, monitored, treated, or diagnosed,
- prescription versus over-the-counter use,
- part of the body or type of tissue applied to or interacted with,
- frequency of use,
- physiological purpose (e.g., removes water from blood, transports blood, etc.), and
- patient population.

The indications for use are normally found in the indications section of the labeling, but indications may also be inferred from other parts of the labeling, such as the precautions, warnings, or the bibliography sections. In some instances, a change in the indications for use

[33] 21 CFR 801.4 "Meaning of *intended uses*."
[34] 21 CFR 814.20(b)(3)(i).

may be a new intended use for the device, in which case, the device would not be substantially equivalent and a premarket approval application or a reclassification petition would be necessary.[35]

Manufacturer: For the purposes of this document, the term manufacturer includes any 510(k) holder, even if that person does not actually fabricate the existing device.

Notified Body: A notified body is a third party designated by EU Member States. A notified body is responsible for verifying manufacturer compliance with regulatory requirements and issuing certifications of device manufacturer competence to produce and release medical devices that are compliant with medical device regulations.

Predicate Device: A legally marketed medical device not subject to premarket approval, to which a 510(k) device may be compared for determinations of substantial equivalence. A 510(k) device must be substantially equivalent to the predicate device to receive premarket clearance.

Substantial Equivalence: For a 510(k) device to be cleared for market, it must be demonstrated to be substantially equivalent to a predicate device in a 510(k) submission. The device must have the same intended use as the predicate device. It also must have either the same technological characteristics as the predicate device or different technological characteristics, and (1) those differences do not raise different questions of safety and effectiveness and (2) the device is at least as safe and effective as the predicate device.[36]

[35] ODE Bluebook Memorandum K86-3 (June 30, 1986), *Guidance on the CDRH Premarket Notification Review Program.*
[36] Section 513(i) of the FD&C Act (21 USC 360c(i)).

Appendix II – Section 604 of FDASIA

SEC. 604. DEVICE MODIFICATIONS REQUIRING PREMARKET NOTIFICATION PRIOR TO MARKETING.

Section 510(n) (21 U.S.C. 360(n)) is amended by—

(1) striking ‘‘(n) The Secretary’’ and inserting ‘‘(n)(1) The Secretary’’; and

(2) by adding at the end the following:

‘‘(2)(A) Not later than 18 months after the date of enactment of this paragraph, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report regarding when a premarket notification under subsection (k) should be submitted for a modification or change to a legally marketed device. The report shall include the Secretary’s interpretation of the following terms: ‘could significantly affect the safety or effectiveness of the device’, ‘a significant change or modification in design, material, chemical composition, energy source, or manufacturing process’, and ‘major change or modification in the intended use of the device’. The report also shall discuss possible processes for industry to use to determine whether a new submission under subsection (k) is required and shall analyze how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices. In developing such report, the Secretary shall consider the input of interested stakeholders.

‘‘(B) The Secretary shall withdraw the Food and Drug Administration draft guidance entitled ‘Guidance for Industry and FDA Staff—510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device’, dated July 27, 2011, and shall not use this draft guidance as part of, or for the basis of, any premarket review or any compliance or enforcement decisions or actions. The Secretary shall not issue—

‘‘(i) any draft guidance or proposed regulation that addresses when to submit a premarket notification submission for changes and modifications made to a manufacturer’s previously cleared device before the receipt by the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate of the report required in subparagraph (A); and

‘‘(ii) any final guidance or regulation on that topic for one year after date of receipt of such report by the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate.

‘‘(C) The Food and Drug Administration guidance entitled ‘Deciding When to Submit a 510(k) for a Change to an Existing Device’, dated January 10, 1997, shall be in effect until the subsequent issuance of guidance or promulgation, if appropriate, of a regulation described in

subparagraph (B), and the Secretary shall interpret such guidance in a manner that is consistent with the manner in which the Secretary has interpreted such guidance since 1997.’’.

Appendix III

Federal Register Notice for the June 13, 2013, Public Meeting on 510(k) Device Modifications

Pages 24 – 29

III. Comments

Interested persons may submit either electronic comments regarding this document to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

IV. Electronic Access

Persons with access to the Internet may obtain the guidance at either *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.regulations.gov.*

Dated: May 2, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–10889 Filed 5–7–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0001]

Microbiology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Microbiology Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on FDA's regulatory issues.

Date and Time: The meeting will be held on June 13, 2013, from 8 a.m. to 6 p.m.

Location: Hilton Washington DC North/Gaithersburg, Salons A, B, C and D, 620 Perry Pkwy., Gaithersburg, MD 20877. The hotel's telephone number is 301–977–8900.

Contact Person: Shanika Craig, *Shanika.Craig@fda.hhs.gov,* Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301–796–6639, Food and Drug Administration, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area). A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the Agency's Web site at *http://www.fda.gov/AdvisoryCommittees/default.htm* and scroll down to the appropriate advisory committee meeting link, or call the advisory committee information line to learn about possible modifications before coming to the meeting.

Agenda: On June 13, 2013, the committee will discuss and make recommendations regarding the possible reclassification of influenza detection devices, currently regulated as class I. The committee's discussion will involve making recommendations regarding regulatory classification to either confirm class I or reclassify these devices into class II with special controls. The committee will address issues such as device performance and public health impact to determine whether special controls are needed to ensure the safety and effectiveness of these tests through their total product life cycle. The proposed special controls will be discussed to support the possible reclassification.

FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at *http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm.* Scroll down to the appropriate advisory committee meeting link.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person on or before June 4, 2013. Oral presentations from the public will be scheduled between approximately 1 p.m. and 2 p.m. Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before May 30, 2013. Time allotted for each presentation may be limited. If the number of registrants requesting to speak is greater than can be reasonably accommodated during the scheduled open public hearing session, FDA may conduct a lottery to determine the speakers for the scheduled open public hearing session. The contact person will notify interested persons regarding their request to speak by May 31, 2013.

Persons attending FDA's advisory committee meetings are advised that the Agency is not responsible for providing access to electrical outlets.

FDA welcomes the attendance of the public at its advisory committee meetings and will make every effort to accommodate persons with physical disabilities or special needs. If you require special accommodations due to a disability, please contact AnnMarie Williams, Committee Management Staff, at *annmarie.williams@fda.hhs.gov* or 301–796–5966, at least 7 days in advance of the meeting.

FDA is committed to the orderly conduct of its advisory committee meetings. Please visit our Web site at *http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm111462.htm* for procedures on public conduct during advisory committee meetings.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: May 3, 2013.

Peter Lurie,

Acting Associate Commissioner for Policy and Planning.

[FR Doc. 2013–10891 Filed 5–7–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0430]

510(k) Device Modifications: Deciding When To Submit a 510(k) for a Change to an Existing Device; Public Meeting; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing the public meeting entitled ''510(k) Device

Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device.'' The focus of this meeting is FDA's interpretation of its regulations concerning when a modification made to a 510(k)-cleared device requires a new 510(k) submission.

DATES: The meeting will be held on June 13, 2013, from 9 a.m. to 5 p.m. EDT.

ADDRESSES: The meeting will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993–0002. Entrance for the public meeting participants (non-FDA employees) is through Building 1 where routine security check procedures will be performed. For parking and security information, please refer to *http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm.*

FOR FURTHER INFORMATION CONTACT: For technical information: Michael J. Ryan, Center for Devices and Radiological Health, Food and Drug Administration, 301–796–6283, email: *michael.ryan@fda.hhs.gov.* For registration questions: Joyce Raines, Center for Devices and Radiological Health, Food and Drug Administration, 301–796–5709, email: *joyce.raines@fda.hhs.gov.*

Registration: Registration is free and available on a first-come, first-served basis. Persons interested in attending this meeting must register online by 5 p.m. EDT, May 30, 2013. Early registration is recommended because facilities are limited and, therefore, FDA may limit the number of participants from each organization. If time and space permits, onsite registration on the day of the meeting will be provided beginning at 8 a.m.

If you need special accommodations due to a disability, please contact Joyce Raines, 301–796–5709 or email: *joyce.raines@fda.hhs.gov* no later than 5 p.m. EDT, May 30, 2013.

To register for the meeting, please visit FDA's Medical Devices News & Events—Workshops & Conferences calendar at *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htm.* (Select this meeting from the posted events list.) Please provide complete contact information for each attendee, including name, title, affiliation, address, email, and telephone number. Those without Internet access should contact Joyce Raines to register (see *Contact Persons*). Registrants will receive confirmation after they have been accepted. You will be notified if you are on a waiting list.

Streaming Webcast of the Meeting: This meeting will also be available via Webcast. Persons interested in viewing the Webcast must register online by May 30, 2013, 5 p.m. EDT. Early registration is recommended because Webcast connections are limited. Organizations are requested to register all participants, but to view using one connection per location. Webcast participants will be sent technical system requirements after registration and will be sent connection access information after May 31, 2013. If you have never attended a Connect Pro event before, test your connection at *https://collaboration.fda.gov/common/help/en/support/meeting_test.htm.* To get a quick overview of the Connect Pro program, visit *http://www.adobe.com/go/connectpro_overview.* (FDA has verified the Web site addresses in this document, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

Requests for Oral Presentations: This meeting includes a public comment session and topic-focused sessions. During online registration you may indicate if you wish to present during a public comment session or participate in a specific session, and which topics you wish to address. FDA has identified general topics in this document. FDA will do its best to accommodate requests to make public comments and participate in the focused sessions. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations, and request time for a joint presentation, or submit requests for designated representatives to participate in the focused sessions. Following the close of registration, FDA will determine the amount of time allotted to each presenter and the approximate time each oral presentation is to begin, and will select and notify participants by June 3, 2013. All requests to make oral presentations must be received by the close of registration on May 30, 2013, 5 p.m. EDT. If selected for presentation, all of your presentation materials must be emailed to Michael Ryan (see *Contact Persons*) no later than June 6, 2013. No commercial or promotional material will be permitted to be presented or distributed at the meeting.

Comments: FDA is holding this meeting to obtain information on its interpretation of the 510(k) device modifications regulations, and specifically, deciding when a 510(k) should be submitted for a change to a 510(k)-cleared device. To permit the widest possible opportunity to obtain public comment, FDA is soliciting either electronic or written comments on all aspects of the meeting topics. FDA would like to receive these comments by May 30, 2013, so they can be discussed during the meeting; however, comments related to this meeting will be accepted until July 13, 2013.

Regardless of attendance at the meeting, interested persons may submit written comments regarding this document to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, or electronic comments to *http://www.regulations.gov.* It is necessary to send only one set of comments. Identify comments with the docket number found in brackets in the heading of this document. In addition, when responding to specific questions as outlined in section II of this document, please identify the question you are addressing. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

Transcript: Please be advised that as soon as a transcript is available, it will be accessible at *http://www.regulations.gov.* It may be viewed at the Division of Dockets Management (see *Comments*). A transcript will also be available in either hardcopy or on CD–ROM after submission of a Freedom of Information Act request. Written requests are to be sent to the Division of Freedom of Information (ELEM–1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857. A link to the transcript will also be available approximately 45 days after the meeting on the Internet at *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htm.* (Select this meeting from the posted events list.)

SUPPLEMENTARY INFORMATION:

I. Background

The Food and Drug Administration Safety and Innovation Act (FDASIA) became law on July 9, 2012. FDASIA added section 510(n)(2) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360(n)), which requires FDA to withdraw its 2011 draft guidance, ''Deciding When to Submit a 510(k) for a Change to an Existing Device,'' and states that the 1997 final guidance of the same name shall be in effect until FDA issues a guidance or a regulation on the topic. Section 510(n)

further requires FDA to submit a report not later than 18 months after the enactment of FDASIA to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate on when a new 510(k) should be submitted to FDA for a modification or change to a legally marketed device. Under this provision, the report must address the interpretation of several phrases in 21 CFR 807.81(a)(3) (the regulation governing submission of 510(k)s for changed or modified devices), possible processes for industry to use to determine whether a new 510(k) is required, and how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices. FDA is holding this public meeting to solicit input on these issues from all interested stakeholders.

II. Topics for Discussion at the Meeting

FDA invites public input on its interpretation of its regulations concerning when a new 510(k) is required for a change to a 510(k)-cleared device. This input will be used to formulate FDA's report to Congress, as well as any future guidance on this topic. FDA would like to solicit comments on the following policy options, both in the form of submissions to the docket for this **Federal Register** notice and in discussion during the public meeting. Please note that implementation of some of these options may require regulatory changes beyond a guidance document.

A. Risk Management

Industry members have proposed use of risk management in the decision process on whether a medical device modification requires a new 510(k) submission. FDA would like to solicit specific, detailed, and practicable proposals that incorporate risk management into this decision process in a way that ensures appropriate and consistent modification decisions by industry and FDA staff. Appropriate decisions in this context are those that allow for both medical device innovation and effective FDA oversight of device changes. Consistent results are a key consideration, as these decisions must be made by many different types of medical device companies and by different FDA review divisions. Inconsistent decisions will make policy unclear and unpredictable for those making future decisions. Proposals must ensure consistency of 510(k) modifications policy, and address and resolve the following concerns.

1. Risk Management is a Process—Published risk management standards and guides, such as the International Organization of Standardization's (ISO's) 14971:2007, ''*Medical devices—Application of risk management to medical devices,*'' are not designed to produce a determination on whether a modified device requires a 510(k). How can risk management be tied to a decision on whether a modification requires a new 510(k)? More specifically, how can FDA tie risk management to the decision that a change or modification in a device is one that could significantly affect the safety or effectiveness of the device? Provide examples of different devices and how the suggested tie between risk management and 510(k) modifications would result in consistent decision making.

2. There are Many Different Ways to do Risk Management—FDA's risk analysis process is described in the preamble to 21 CFR part 820, the Quality System Regulation, at 61 FR 52620 (October 7, 1996), in the response to comment 83. Although FDA's risk analysis process is similar to some documented risk management processes, there are many other ways to conduct risk management and still meet FDA requirements. Even ISO 14971, one of the more common risk management guides, allows for flexibility in its processes such that different manufacturers following ISO 14971 could conceivably reach different risk management decisions for similar device changes. How can a single risk management process be chosen that leads to consistent and appropriate decisions on whether a 510(k) is required for a device modification?

3. Risk Management Analyses Inherently Involve Subjectivity—Risk management requires the manufacturer to: (1) Establish ''criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk,'' (2) predict known and foreseeable hazards associated with the device, (3) estimate the risks for each hazard, and (4) evaluate the risks of each associated hazard using the manufacturer's established criteria. ISO 14971. FDA is not aware of universally accepted risk acceptability criteria for medical devices. Furthermore, it is often difficult to find objective data to help determine frequency and even severity of risk, which often leads to inconsistent risk analyses. How can the inherent subjectivity of risk management be controlled to ensure consistent and appropriate decisions on whether a 510(k) is required for a device modification?

4. A Company's Risk Management Processes are Contained Within its Overall Quality System and May Not be Specifically Scrutinized by FDA During 510(k) Reviews—To consider integration of risk management in the 510(k) modification decision-making process, FDA must have assurance that a company's risk management process is comprehensive and appropriately implemented. How can FDA obtain such assurance?

B. Reliance on Design Control Activities

FDA is soliciting proposals for how industry and FDA could utilize design control activities such as design verification and validation to ensure that device modifications are appropriately evaluated prior to marketing. FDA would need some form of effective oversight in this process to properly perform its function of protecting the public health. The Agency would need the opportunity to review design control activities when necessary because improper application of these activities may lead to incomplete or inaccurate evaluations of design changes and the marketing of unsafe or ineffective devices. At this time, FDA generally reviews design control information for 510(k)-eligible devices only during inspections, and inspections do not necessarily focus on the specific information (such as design specifications, testing protocols, etc.) that FDA needs to review to ensure that design changes are properly evaluated. Inspection resources are also limited. Any proposal for reliance on design control activities as part of FDA's 510(k) modifications policy should consider how FDA may ensure effective oversight. Input on the following specific questions is requested.

1. FDA Does Not Typically Review Design Control Information Prior to Marketing Clearance and Resource Issues, Among Other Things, Limit the Extent of its Review of Design Control Information—How can FDA ensure that design control activities will limit the potential for marketing of device modifications that may be unsafe or ineffective?

2. Although 21 CFR 820.30 Imposes the Same Design Control Requirements on All Medical Device Manufacturers, the Ways in Which Manufacturers Comply with These Requirements Vary—How can FDA ensure consistency in use of design controls to ensure that only safe and effective modified devices are marketed?

C. Critical Specifications

Industry members have proposed the use of critical specifications, a new concept, to make decisions on whether a 510(k) is required for a device modification easier. This concept would be one way that FDA could link use of design control activities to 510(k) modification decisions.

Under this proposal, if FDA and manufacturers can identify essential device specifications—critical specifications—and can agree on limits and testing protocols for those specifications within a 510(k), then a device manufacturer may make modifications to a device, and as long as the resulting device remains within the agreed-upon limits for all of the critical specifications, no new 510(k) would be required for that modified device. This approach could allow FDA to rely on the quality system regulation to ensure that qualifying changes could not significantly affect safety and effectiveness because there was no change to a critical specification. FDA would like to discuss the feasibility of this approach, both for manufacturers and FDA's review staff, and how it might be implemented. It is important to note that this approach would not apply to changes to intended use or labeling, as those aspects of a device are not associated with specifications.

Critical specifications could include a range of technological and material design aspects, such as dimensional specifications, shelf life, or material purity. Critical specifications would necessarily be device specific, so it would be impossible to identify all of the possible specifications in guidance, although FDA guidance could note useful examples. To qualify as a critical specification, FDA and the 510(k) submitter would have to agree on the identity and parameters of a critical specification within a 510(k) review. The manufacturer would have to clearly identify types of changes that might be made, which specifications it would designate as critical for those types of changes, and specification bounds or tolerances. For example, if a manufacturer anticipates possible changes in materials for an implant (e.g., due to supplier changes that may occur post-clearance), then it might wish to designate tensile strength of the material as a critical specification. It would then set parameters for properties that the new material needs to meet; for instance, tensile strength must be 950 MPa ± 15 MPa (megapascals). The 510(k) would also describe how tensile strength would be tested. FDA reviewers would need to consider whether any other properties should be identified as critical specifications for the type of change in question, and whether appropriate test methods have been identified to ensure the modified device will meet its critical specifications. Voluntary consensus standards (such as those recognized on FDA's Web site in its recognized standards database at *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm*) could be used to determine critical specifications and their parameters or testing protocols. If critical specifications are agreed on prior to 510(k) clearance, then a manufacturer who modifies its device after clearance would be able to do so without submission of a new 510(k) as long as the agreed-upon verification and validation activities show those critical specifications are unchanged.

To take advantage of this approach, manufacturers would have to identify the following in their 510(k) submissions:

- A list of potential changes that might be made;
- Critical specifications for each change: Those device specifications—physical, material, or performance—that are essential to safe and effective use of the device (e.g., tensile strength);
- Bounds for those specifications that a changed device must remain within (e.g., 950 MPa ± 15 MPa); and
- The verification and validation test protocols that will be used to examine those specifications pre- and post-modification, within the rubric of the quality system regulation.

FDA's review staff would be responsible for reviewing the above information and determining whether a change that results in a device that remains within the identified specifications could significantly affect safety or effectiveness.

FDA is soliciting input on the feasibility of the critical specifications approach and proposals for how FDA could implement such a program. Input on the following specific questions is requested.

1. How could critical specifications be incorporated into FDA's review process? Review of critical specifications proposals in 510(k)s will require additional review time and resources. How should situations where agreement cannot be reached within review timeframes be handled? How could situations where FDA is ready to proceed with a substantial equivalence decision, but critical specifications have not been agreed upon, be handled?

2. How could critical specifications agreements be documented? Should they be summarized in 510(k) Summaries or substantial equivalence letters?

3. Should use of critical specifications be limited to certain types of changes? If so, which ones?

4. Are there particular specifications that could be deemed critical for all devices? If so, which ones?

5. Could critical specifications be implemented as an optional paradigm? This approach could potentially be implemented as an optional approach that manufacturers could use where it is most efficient; manufacturers that chose not to identify critical specifications in a 510(k) would then be subject to the current 510(k) modifications decision-making paradigm. Please discuss the practical implications of this approach.

D. Risk-Based Stratification of Medical Devices for 510(k) Modifications Purposes

FDA is seeking comments on the practicality of stratifying device types that require 510(k)s by risk. Under such a framework, FDA would expect 510(k)s for modifications of higher risk devices that meet the standard in 21 CFR 807.81(a)(3). For lower risk devices, FDA would not expect 510(k)s for all modifications that meet the standard in 807.81(a)(3). However, because modifications to lower risk devices could still result in harm or injury, FDA would expect 510(k)s for certain modifications (for example, changes to the indications for use) even if the device is lower risk. FDA could require some other measure, such as periodic reporting, for modifications of lower risk devices that are not submitted in 510(k)s. This approach would allow FDA to focus review resources on areas that are more important from a public health perspective. Comments on this approach should address the following questions.

1. How should FDA delineate higher versus lower risk devices? For example, would higher risk devices include only those designated as life sustaining, life supporting, or implants?

2. Should FDA require some other measure, such as periodic reports, for modified lower risk devices in lieu of 510(k) submissions?

3. Because modifications to lower risk devices could still result in harm or injury, FDA believes that some modifications to lower risk devices should still be reviewed in 510(k) submissions prior to marketing. How should FDA delineate which lower risk device modifications require 510(k)s and which do not?

E. Periodic Reporting

FDA is soliciting comments on the advisability of requiring periodic reporting for modifications to 510(k)-cleared devices that do not require new 510(k) submissions. FDA does not typically review 510(k) modifications decisions that do not result in 510(k) submissions, unless that information is specifically looked at during an inspection or submitted in conjunction with future changes that do require a 510(k). If manufacturers were required to submit periodic reports identifying and describing their design changes that did not result in 510(k) submissions, FDA would then review these changes and ensure that decisions were made appropriately. This process would likely be similar to annual reporting of device changes for approved class III devices. Over time, periodic reporting would give FDA a more complete picture of the changes industry is making to 510(k)-cleared devices, and may allow FDA to tailor 510(k) modifications requirements to ensure that the Agency is reviewing only the changes it needs to in new 510(k) submissions. Review of periodic reports, however, would require additional FDA resources. Comments on periodic reporting should address the following questions.

1. How often should FDA require periodic reports, e.g., annually, biannually, etc.?

2. Should FDA require periodic reports for all 510(k) devices or only certain devices? If not all devices, then which ones?

3. What information should be included in a periodic report?

F. Other Policy Proposals

FDA acknowledges that any one of the above options may be insufficient on its own; if any changes are made to FDA's 510(k) modification policy, the Agency may adopt a combination of those options. FDA also acknowledges that other options may exist that have not been identified above. FDA is therefore soliciting any other proposals for revising the Agency's 510(k) modification policy. Any policy must ensure:

- Consistent decision-making by both industry and FDA;
- Adequate control of device modifications that could significantly affect safety or effectiveness; and
- Effective FDA oversight of modifications to 510(k)-cleared devices to adequately protect the public health and allow for medical device innovation.

Proposals should be as detailed and specific as possible, and should take into account the issues discussed above in the individual options.

G. Examples

In addition to the options discussed above, FDA is seeking specific examples of device changes that manufacturers have made that should not trigger the requirement for a new 510(k) submission, with explanations as to why 510(k) submissions should not be required. These examples will help FDA develop an appropriate 510(k) modifications policy. FDA typically sees only those device modifications that result in new 510(k) submissions; device changes that do not result in new 510(k) submissions generally are not reviewed by the Agency. Industry provision of these changes will help inform FDA's 510(k) modifications interpretation.

Examples of device changes may also be used for discussion during this public meeting. All examples discussed publicly will be de-identified. Examples may be submitted to the Agency in de-identified form through third parties such as trade associations.

Dated: May 2, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–10888 Filed 5–7–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Summary of Responses To Request for Information (RFI): Opportunities To Apply a Department of Health and Human Services Message Library To Advance Understanding About Toddler and Preschool Nutrition and Physical Activity

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Summary of Responses to Request for Information (RFI).

SUMMARY: On January 29, 2013, the Health Resources and Services Administration (HRSA) issued a *Request for Information (RFI)* to solicit ideas and information related to ways in which the U.S. Department of Health and Human Services (HHS) can work with interested partners to disseminate and apply *TXT4Tots,* a library of short, evidence-based messages on nutrition and physical activity targeted to parents, caregivers, and health care providers of children ages 1–5 years. HRSA released the *TXT4Tots library* in English and Spanish on February 19, 2013; and followed with an Open Forum on February 20, 2013, to provide further opportunity for input on dissemination and application of the library of messages. HHS received over 25 written responses to the RFI, and approximately 100 individuals participated in the Open Forum.

Comments and Responses: The written responses to the RFI as well as the comments received through the Open Forum indicate that TXT4Tots aligns with the activities of many existing organizations and programs. Several of the respondents expressed an interest in collaborative opportunities to incorporate the messages into current outreach and educational efforts. Some examples of current programs that could leverage the TXT4Tots messages include initiatives at the federal, state, and local levels. The majority of the suggested organizations and programs focus on promoting healthy choices for children and their families. Recommendations included integrating the TXT4Tots messages into their programs and services or using the internet to disseminate the information through Web sites and social media.

Respondents also emphasized that mobile health, social media, and other innovative strategies are a valuable resource to reach a diverse population and can be effectively leveraged to support equitable access to health information. With regard to vehicles for dissemination of the TXT4Tots messages, respondents suggested that they needn't be complicated, but should be user friendly. In addition, respondents noted that the most effective tools for dissemination are those that can fully engage the end users. Specific suggestions for dissemination of the TXT4Tots messages included social media, existing tools and applications, existing Web sites and web services, and text messages, as well incorporating messages into baby product packaging, curricula, health fairs, emails, newsletters, and print materials. Emphasis was placed on leveraging existing platforms that promote healthy choices for young children and could readily integrate the TXT4Tots message content. Respondents also recommended that the TXT4Tots messages be linked to additional sources of information; for example, if utilized as a text message program, URLs could be included to link the message recipients to Web sites with additional information. In addition, social media posts could link to Web sites with ideas for healthy recipes and age-appropriate activities to compliment the messages.

Appendix IV

Inspection Documentation Examples

Pages 30 – 37

[redacted]

PRODUCT RELEASE FORM

Product/Package Name: [redacted]
Application Name and Version [redacted]

Software intended to permit the transfer, review, and archiving of diagnostic image data.

Release Date: Sept. 20, 2010

SIGNATURES

By signing this sheet, the undersigned attest to the fact that the accompanying documents are complete and accurate, and that all specified procedures, including risk analysis, have been [redacted]

[redacted]

[redacted]

[redacted]

[redacted] Design Document

[redacted]

[redacted]

Revision History

Rev.	Date	Author	Reason for Change
1.0	09/20/2010	met	Original
2.0	09/20/2010	met	**Formal Design Review by:** [redacted]

[redacted]

1. Overview

2. Functional Specifications

This is a defect correction release, primarily for the [redacted] component, but including changes to [redacted] No changes were made affecting design, features, etc.

See Appendix A for detailed description of changes.

3. User Interface and Documentation

The user interface was not changed in any component application for this release.

4. Implementation

As described in detail in Appendices.

5. Testing

As described in detail in Appendices.

6. FDA 510 (K) Pre-Market Notification In the review of the changes incorporated in this design document, we have asked and answered the following questions:

Do the changes incorporated in this design affect indications for use? _NO_ _ _ (yes or no)

Are clinical data necessary to evaluate safety and effectiveness for purposes of determining substantial equivalence? _YES_ _ _ (yes or no)

Do results of design validation raise new issues of safety and effectiveness? _ _NO_ _ (yes or no)

It is the view of [redacted] that 510 (K) Pre-Market Notification of this development is not

[redacted]

PRODUCT RELEASE FORM

Product/Package Name: [redacted]
Application Name and Version (versions unified: [redacted]

Release Date: Oct. 14, 2010

SIGNATURES

By signing this sheet, the undersigned attest to the fact that the accompanying documents are complete and accurate, and that all specified procedures, including risk analysis, have been implemented.

[redacted]

[redacted]

[redacted] Design Document

[redacted]

Revision History

Rev.	Date	Author	Reason for Change
1.0	10/14/2010	met	Original
2.0	10/14/2010	met	**Formal Design Review by:** [redacted]

[redacted]

1. Overview

2. Functional Specifications

This is a defect correction release, primarily for the [redacted] component, but including changes to [redacted] and one correction for [redacted] access to all components which access the [redacted] No changes were made affecting design, features, etc.

See Appendix A for detailed description of changes.

3. User Interface and Documentation

The user interface was not changed in any component application for this release.

4. Implementation

As described in detail in Appendices.

5. Testing

As described in detail in Appendices.

6. FDA 510 (K) Pre-Market Notification In the review of the changes incorporated in this design document, we have asked and answered the following questions:

Do the changes incorporated in this design affect indications for use? NO (yes or no)

Are clinical data necessary to evaluate safety and effectiveness for purposes of determining substantial equivalence? NO (yes or no)

Do results of design validation raise new issues of safety and effectiveness? No (yes or no)

[redacted]

It is the view of [redacted] that 510 (K) Pre-Market Notification of this development is not required.

7. Risk Assessment

These changes do not change the overall or specific risk in the [redacted] Product, a new risk management report is not required.

Design Document Approval

[redacted]

Appendix A - Detailed List of Enhancements.

[redacted] Release Detail Report [redacted]

Detail report of tickets included for specified component and milestone. Example URL:

[redacted]

Ticket	Summary	Created	Type	Severity
Description				
[redacted]	Possible crash of [redacted] components if [redacted] file exists and [redacted] file does not.	09/23/10	defect	Minor

Possible crash of [redacted] components if [redacted] file exists and [redacted] file does not.

Found in [redacted]

Steps to Reproduce:

[redacted]

[redacted]

Ticket	Summary	Created	Type	Severity
Description				
[redacted]	Lossless JPEG DICOM improper decode in [redacted]	06/12/09	defect	Minor

[redacted]

Text for this trac entry comes from [redacted] which follows:

[redacted]

EXHIBIT #4 page 3 of 3

Ticket [redacted] (new defect)

Lossless JPEG DICOM improper decode in [redacted]

Opened 1 year ago
Last modified 6 days ago

Reported by:	[redacted]	Assigned to:	[redacted]
Priority:	major	Milestone:	[redacted]
Component:	[redacted]	Version:	[redacted]

MAIN FLOWCHART
WHEN TO FILE A 510(k) AFTER CHANGE TO A LEGALLY MARKETED DEVICE

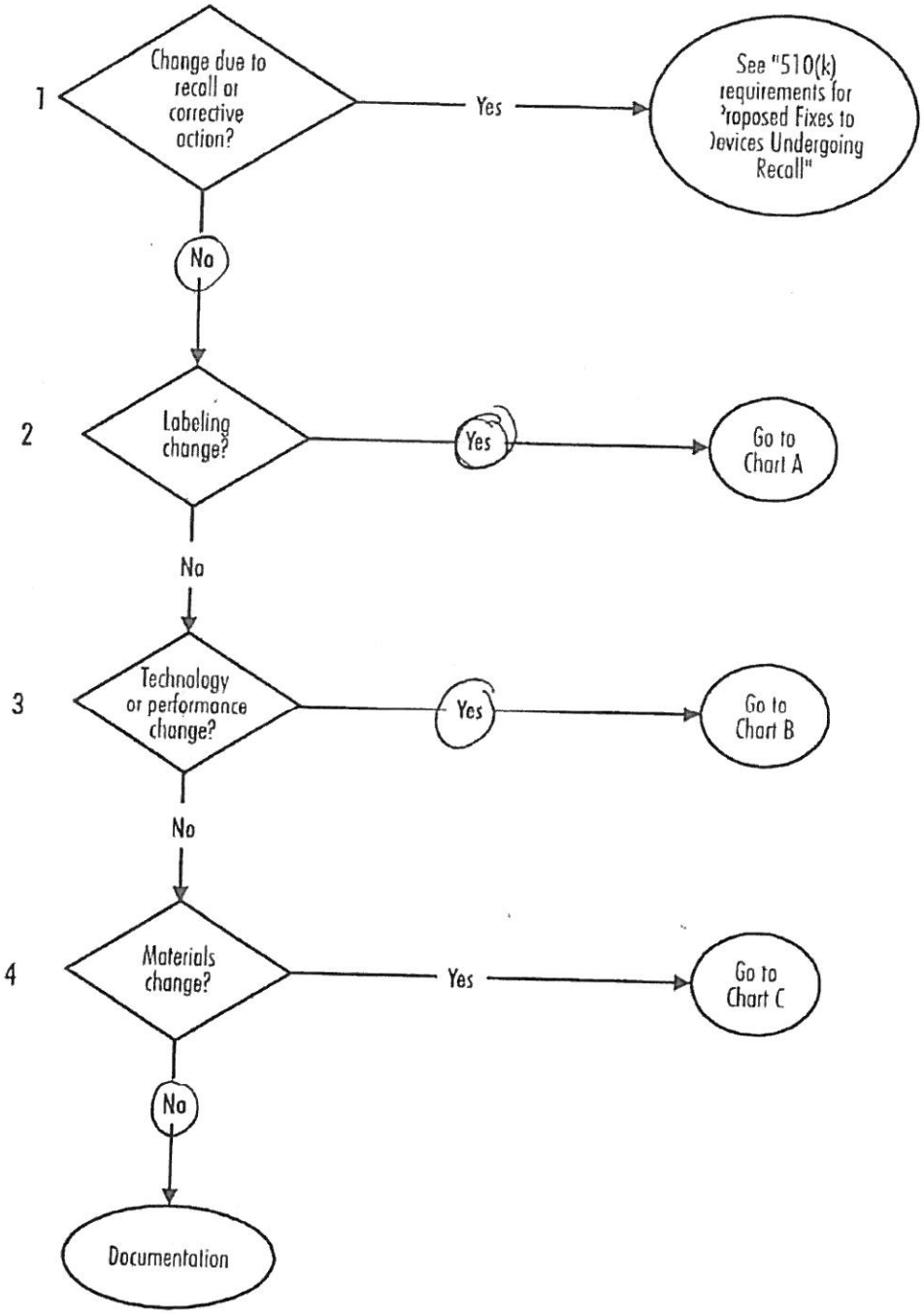


Exhibit # 1, page 1 of 3

[redacted]

FLOWCHART A - IS IT A LABELING CHANGE?

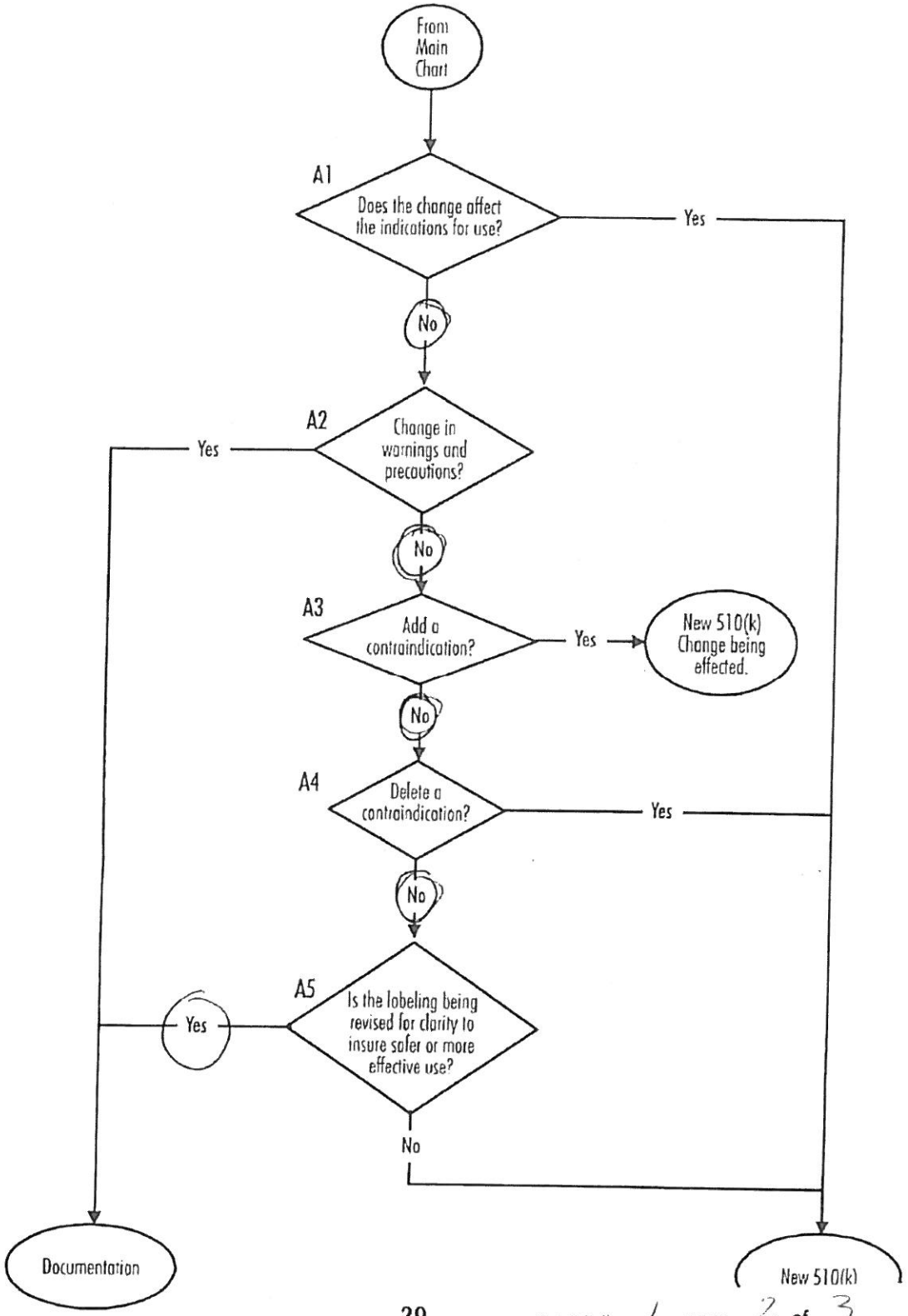


Exhibit # 1, page 2 of 3

[redacted]

FLOWCHART B - IS IT A TECHNOLOGY OR PERFORMANCE CHANGE?

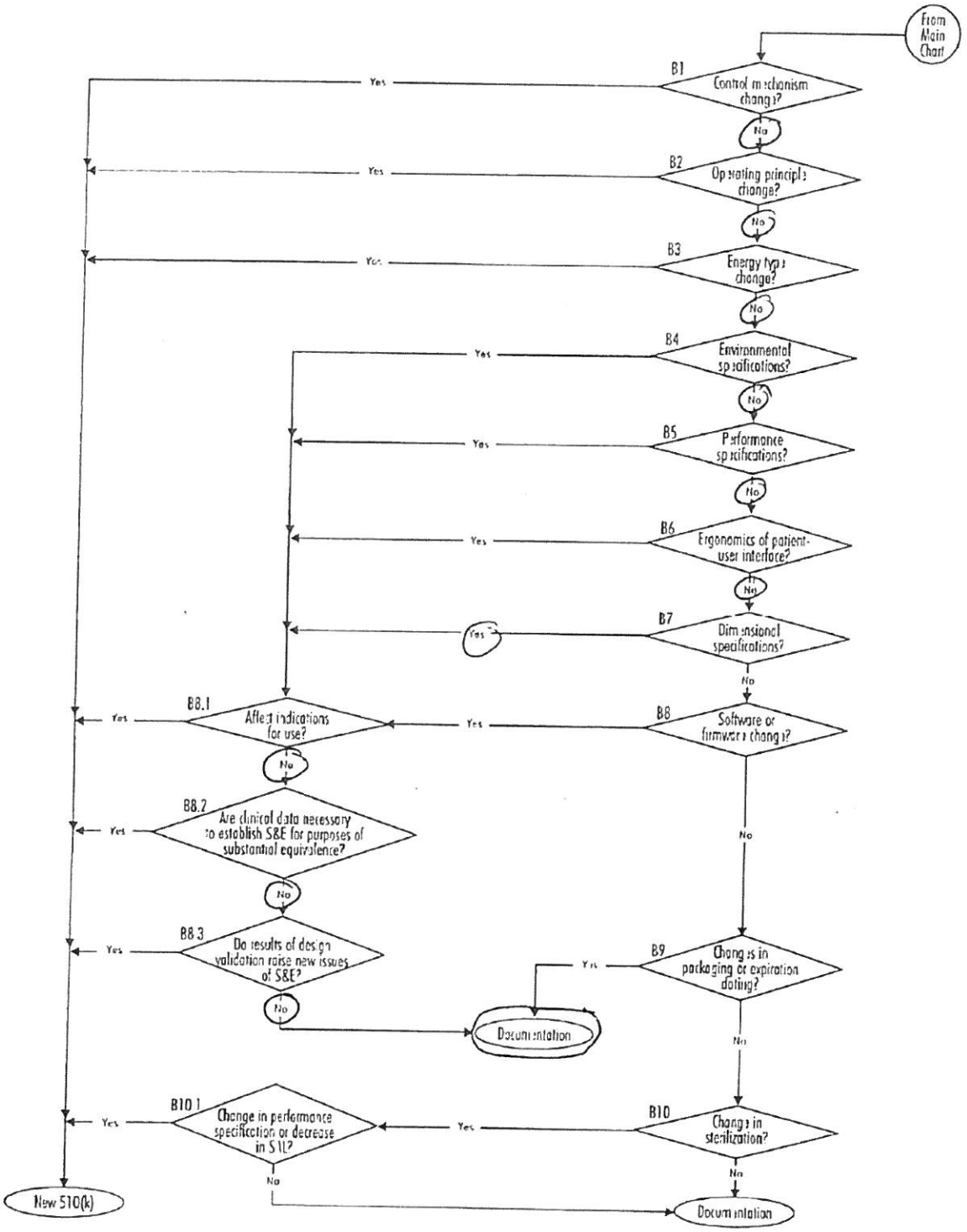


Exhibit # 1, page 3 of 3

[redacted]

Appendix V

1997 510(k) Device Modifications Guidance

Pages 38 – 82

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

510(k) Memorandum #K97-1

Date JAN 10 1997

From Director, Office of Device Evaluation

Subject **Deciding When to Submit a 510(k) for a Change to an Existing Device**

To ODE Review Staff
Through: ODE Branch Chiefs

Purpose

The purpose of this guidance is to provide direction to manufacturers on deciding when to submit a 510(k) for a change to an existing device.

Background

On April 8, 1994, FDA circulated for comment the first draft guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device." This draft was the subject of a May 12, 1994, FDA video conference and it was the subject of several trade and industry association meetings. As a result of these activities, FDA received over 60 comments on this version of the guidance. On October 16, 1995 FDA published a Notice of Availability in the Federal Register announcing the availability of an August 1, 1995 draft of this guidance.

Attached is the final version of the guidance for reference by the review staff. This guidance is not intended to supplant existing definitive guidance for modifications to specific devices, e.g., daily wear contact lenses. Moreover, the guidance is not intended to apply to combination products, such as drug/device or biologic/device combinations, although it may be helpful. The guidance is also not intended to address the need for submitting a 510(k) by remanufacturers of devices. FDA intends to develop additional guidance specific to these situations.

Procedures

The type of modifications addressed in the draft guidance include labeling changes, technology or performance specifications changes, and materials changes. **When making the decision on whether to submit a 510(k)**, the manufacturer's basis for comparison of any changed device should be the device described by the cleared 510(k) or to their legally marketed preamendments device. That is, manufacturers may make a number of changes without having to submit a 510(k), but each time they make a change, the device they should compare it to is

their most recently cleared device (or their preamendments device). In effect, manufacturers need to submit a new 510(k) only when a change, or the sum of the incremental changes exceeds the §807.81(a)(3) threshold, "could significantly affect the safety or effectiveness of the device."

Because many simultaneous changes may be considered in the evolution of device design, each type of change should be assessed separately. **When any one change leads the manufacturer to decide to submit a 510(k)**, then a 510(k) requesting the change should compare the modified device to a legally marketed device (the manufacturer's device or a competitor's legally marketed device). In the instance where the legally marketed device is the manufacturer's own device, the 510(k) should identify previous changes that did not necessitate a 510(k) submission, to avoid confusion when we compare the current 510(k) to the previous clearance.

The guidance includes a main flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on when to submit a 510(k) for a change to an existing device. The flowchart includes the following three logical breakouts of changes that might be made to a device: labeling changes, technology or performance specifications changes, and materials changes. To use the model, the questions posed in the flowchart should be answered until the 510(k) holder is directed to: (1) consider submitting a 510(k) (including a new 510(k) labeled "change being effected"), or (2) document the decision-making.

When contemplating changes to a device, manufacturers should use the flowchart for each individual type of proposed change, e.g., performance specification change, material change, etc. If a manufacturer's consideration of all proposed changes results in a decision merely to document the decision-making, they should document the application of the model along with the necessary records of the validation of changes to the device. In those circumstances where the proposed change is not addressed in the flowchart or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to find out whether other, specific guidance exists or if additional help is available.

Effective Date:

This guidance is effective immediately.

for Susan Alpert, Ph.D. M.D.

Deciding When to Submit a 510(k) for a Change to an Existing Device

This document is intended to provide guidance in the preparation of a regulatory submission. It does not bind the FDA or the regulated industry in any manner.

Office of Device Evaluation
Document Issued On: January 10, 1997

Note: While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by contacting the Premarket Notification (510(k)) Section at 301-796-5640. For questions regarding the use or interpretation of this guidance, also contact the Premarket Notification (510(k)) Section at 301-796-5640.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

Preface

On April 8, 1994, FDA circulated for comment the first draft of a document intended to provide guidance to manufacturers on when to submit a new 510(k) for changes to an existing device. That draft was the subject of an FDA/FDLI video conference on May 12, 1994, and also was the subject of discussion at several trade and industry association meetings. Subsequently, in response to comment letters, a second draft of the guidance (dated August 1, 1995) was developed and made available for additional public comment through publication of a Notice of Availability in the Federal Register (60 FR 53624, October 16, 1995). These comments from the second round of public review have led to the current guidance document.

While we are pleased to issue this guidance in final form, we recognize that, as a guidance document, it can and will need to be revised over time as we gain more experience with its application. These revisions will be based on comments and recommendations of its users, both in the industry and in FDA. CDRH continues to look at the 510(k) Program and ways of reengineering the review process. For example, a program to pilot test the third party review of 510(k)s was begun in the summer of 1996. In addition, we will be looking at the better use of consensus standards and special controls in the 510(k) review, as well as ways to better integrate compliance with design controls under the new Quality Systems Regulation with the 510(k) process.

TABLE OF CONTENTS

SECTION	PAGE
Preface	ii
Introduction	1
The 510(k) Process and Good Manufacturing Practices	2
Scope of the Proposed Guidance	4
Assumptions/Axioms	5
The Model	7
Labeling Changes	9
Technology, Engineering and Performance Changes	12
Materials Changes	16
Materials Changes in *In Vitro* Diagnostic Products	20
Definitions	21
Flowcharts	27
Appendix	32
References	37

Introduction

Almost from the enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act in 1976, FDA staff have attempted to define with greater accuracy when a change in a medical device would trigger the requirement that a manufacturer submit a new premarket notification (510(k)) to the Agency. The regulatory criteria state that a premarket notification must be submitted when:

(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.*[1]

The key issue here is that the phrase "could significantly affect the safety or effectiveness of the device" and the use of the adjectives "major" and "significant" sometimes lead to subjective interpretations. Because of this, manufacturers have frequently expressed the need for more specific guidance in applying the regulatory standard in their decision-making.

Previous attempts to develop such guidance have focused generally on defining broad issues or principles that should be used in deciding when to submit a 510(k). These attempts have been only partially successful in clarifying the situation. The primary reason for partial success is that the variety of device types currently marketed, as well as the myriad changes that occur as technology evolves, are so diverse that one or two unifying principles cannot possibly account for all possible situations.

To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an impossible task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely to keep pace with an ever-changing technology.

Between the two extremes of broad principles and detailed enumeration is the area where models can be developed to assist in the decision-making. If created and used properly, such a model could provide guidance leading toward a rational answer as to whether a 510(k) is necessary in the large majority of circumstances. This document proposes a flowchart model that can be used by manufacturers in their decision-making to analyze how changes in devices may affect safety or effectiveness. In the model, we attempt to address changes to devices at a level detailed enough so that application of the broad principles contained in the regulations would minimize disagreements between manufacturers and the Agency . The goal of the model is to provide guidance in answering a manufacturer's questions on whether a 510(k) should be submitted for a particular type of change and to minimize the number of instances where the answer would be uncertain. Taken as a whole, this guidance, and the model it describes, provides the agency's best definition of when a change to a device could significantly affect safety or effectiveness.

The 510(k) Process and Good Manufacturing Practices

Any guidance on 510(k)s for changes to a marketed device must consider the role the Good Manufacturing Practice (GMP) regulation plays in changes to device design. For some types of changes to a device, the Agency continues to find that a 510(k) is not necessary and that reliance on existing GMP requirements may continue to reasonably assure the safety and effectiveness of the changed device.

It is important to note that the current 1978 GMP regulation does not directly address the original design of a device. In fact, it was the recognition of the need for this type of control for many types of devices that led to the inclusion of pre-production design controls in the Safe Medical Devices Act of 1990.[2] The new GMP and design control regulation, called the Quality Systems regulation[3], will implement the new authority

granted by the Safe Medical Devices Act and require design controls for new devices. The Quality Systems regulation will take effect in two stages. The entire regulation, except for design controls, will take effect on June 1, 1997. The design control provisions will take place on June 1, 1998.

The 1978 GMP regulation, however, is not entirely silent on device design. It requires manufacturers to document in the device master record (§820.181) any changes (and internal approval of changes) to device design and any associated testing (§820.100). It also requires process validation to assure that devices meeting the designed quality characteristics will consistently be produced (§820.5 and §820.100). Finally, manufacturers must have a formal approval procedure for any change in the manufacturing process of a device including those dictated by design changes (§820.100(b)(3)).

The Quality Systems regulation has similar requirements relating to design changes, and these requirements will replace the 1978 GMP requirements on June 1, 1998. Under the Quality Systems regulation, manufacturers are required to review and approve any changes to device design and production (new §820.30 and §820.70) and document changes and approvals in the device master record (new §820.181). Any process whose results cannot be fully verified by subsequent inspection and test must be validated (new §820.75), and changes to the process require review, evaluation, and revalidation of the process where appropriate (new §820.75).

The net effect of the 1978 GMP regulation or the new Quality Systems regulation is to require that, when manufacturers make a change in the design of a device, they must have a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector.[4] Thus, while the Quality Systems regulation requires design controls for many devices, those controls do not take effect until June 1, 1998. Until then, manufacturers must still comply with the current GMP regulation, which imposes requirements on changes to device design. For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on good manufacturing practices (either as implemented under the 1978 GMP or the Quality Systems regulation) to continue to assure the safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision-making based on their testing results or other design validation criteria.

Scope of this Guidance

The guidance outlined in this document has been developed to aid manufacturers of class I, class II or class III devices (for which premarket approval has not yet been required under section 515(b)) who intend to modify their device and are in the process of deciding whether the modification exceeds the regulatory threshold for submission of a new 510(k). This guidance for changes to an existing device is intended to supplement the general guidance on review of 510(k)s contained in the ODE Bluebook memorandum on the premarket notification program.[5]

This document was developed to address all types of modifications, including modifications to device design as well as modifications to device labeling. Furthermore, this guidance can be applied to situations when a legally-marketed device is the subject of a recall and a change in the device or its labeling is indicated. This guidance is not intended to apply, although it may, to combination products, such as drug/device or biologic/device combinations. Furthermore, this guidance is not intended to address the need for submitting 510(k)s by remanufacturers of devices,[6] who do not hold the 510(k) for the device. FDA intends to develop additional guidance specific to these situations at a later date.

This document incorporates existing guidance and policy[7] regarding when 510(k)s are necessary for modifications to a legally-marketed device.[8] In some cases, the existing guidance derives from advice given to only a few manufacturers for a limited number of devices. In such instances, we have attempted to generalize the concepts to apply to a broader range of devices. However, special cases exist where both manufacturers and FDA have worked to establish definitive guidance for modifications to specific devices, e.g., daily wear contact lenses.[9] This guidance is not intended to supplant such existing device-specific guidance but may cover areas not addressed in such device-specific guidance.

Assumptions/Axioms

In developing this guidance for aiding in deciding when to submit a 510(k), a number of assumptions had to be made. Some derive from existing 510(k) policy and are widely known, others are necessary for using the logic scheme contained in this guidance. Thus, anyone using this guidance needs to bear in mind the following assumptions:

- Any person required to register under 21 CFR 807.20, who plans to market a device for the first time, that is not exempt from the requirements of premarket notification, will always have to submit a 510(k). (Note that private label distributors and repackagers are exempt from submitting a 510(k) if they satisfy the requirements of 21 CFR 807.85(b).)

- The guidance should be applied using the intended changes to devices and not any unforeseen results of implementing a change that may be discovered during design validation (although such unforeseen results may impact safety and effectiveness and, thus, may be key in deciding to submit a 510(k)).

- When manufacturers submit a 510(k), they must compare their device to a legally-marketed device that does not require premarket approval. This comparison may be to the manufacturer's own device described in a cleared 510(k), a more recent legally marketed incarnation of that device, another firm's device found substantially equivalent, a reclassified device, or a legally marketed preamendments device. That is, when manufacturers submit a new 510(k), they have a number of options for comparison. However, in using this guidance to help determine whether a particular change requires the submission of a new 510(k), manufacturers should compare the change or changes to their device as previously found to be substantially equivalent. This is particularly necessary so that they may take advantage of the guidance's reliance on using the results of GMP-required activities in deciding when to submit a 510(k). Manufacturers are free to use a system of analysis not described in this guidance where they compare to a competitor's legally-marketed device for an evaluation of the safety or effectiveness of a change, but this guidance is not applicable in such circumstances.

- Because many changes occur in the evolution of a device, each change must be assessed individually, and collectively with other changes made since the last 510(k) clearance. When the effect of any one change, considered together with all previous changes since the last 510(k) clearance, leads a manufacturer to decide it is legally required to submit a new 510(k), then a 510(k) incorporating all the changes and comparing the new device to their legally-marketed device should be submitted. (The manufacturer should distinguish the change that triggers the 510(k) from those changes previously made for which a 510(k) was not required.) Note that this comparison may be done via a table or other means. Once the new 510(k) is cleared, it may form the basis of comparison for when to submit a new 510(k) for the next sequence of changes.

- Whenever manufacturers change their device, they must comply with the GMP regulation unless the device in question is exempt by regulation from the GMP.[10] This regulation requires that specification changes be subject to controls as stringent as those applied to the original design specifications of the device, and that such changes be approved and documented by a designated individual(s). Documentation must include the change approval date and the date the change becomes effective (21 CFR 820.100(a)(2)). This means that when a change is made to the device, there is verification through testing or other appropriate engineering means that the change does not adversely affect the device's safety or effectiveness. Only then can manufacturers assure an accurate assessment of the change(s) in the device when they apply this guidance. They must maintain records of their testing or engineering analysis under the current GMP. It is this validation/analysis of the design changes and the documentation maintained by manufacturers that can support the decision on whether to submit a 510(k).

- To derive maximum benefit from this guidance, manufacturers should have in place a mechanism for evaluating whether a proposed change meets the regulatory threshold for a new 510(k). This mechanism could document use of this guidance, if applicable, or other decision-making aids or bases for deciding whether a 510(k) is necessary.

- This guidance can not address every type of change to every type of device. No matter how carefully this guidance is applied, there will still be decisions in a "gray area" that manufacturers will have to make. If manufacturers notify the Office of Device Evaluation of these instances, this gray area can be better defined and understood, and, ultimately, this guidance can be refined accordingly.

- Manufacturers should understand that, even though they may use this guidance and submit a 510(k), a substantial equivalence determination is not assured. Some changes to a device may be sufficiently significant that the changed device would be determined to be not substantially equivalent and a premarket approval application would be required before the device could be marketed.

The Model

The model uses a flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on whether to submit a 510(k) for a change to an existing device. A single flowchart containing all the logical steps necessary is large and cumbersome and could be quite daunting, Therefore, one is not included in this document. Rather, for ease of use, the single flowchart has been broken down into five smaller flowcharts that include:

- the main types of changes that might be made to a device (Main Flowchart)
- labeling changes (Flowchart A)
- technology or performance specifications changes (Flowchart B)
- materials changes (Flowchart C), and
- materials changes for *in vitro* devices (IVDs) (Flowchart D).

The reader is referred to the Definitions section (page 22) for the meaning of terms used in the flow charts.

To use the model properly, manufacturers must answer the questions posed in the flow chart for **each** individual type of change, e.g., performance specification change, material change, etc., until a decision is made either to consider submitting a 510(k) or to document the basis for concluding that a 510(k) is not necessary. Manufacturers should consult the flowchart that applies to the particular change or modification under consideration. When making the decision on whether to submit a 510(k) for changes, the comparison should be to the device described in the last 510(k) clearance, collectively with the presently legally marketed device which incorporated modifications that did not require premarket clearance by the agency. One must keep in mind that what may on the surface appear to be one discrete change to a device may involve multiple changes of various types, triggering submission of a new 510(k).

If any one of the changes that is analyzed results in a manufacturer's decision to submit a 510(k), then the 510(k) should incorporate all of the planned changes, as well as a comparison of the changed device to their legally-marketed device. (If a manufacturer has a cleared 510(k), reference to it will aid in the evaluation of the new 510(k).) If a manufacturer's consideration of all planned changes results in a decision merely to document the decision-making, it should document the application of the model along with the necessary records of the validation of all changes to the device. In addition, a manufacturer may also compare their device to a competitor's legally marketed device.

For those circumstances where the proposed change is not addressed in the flowcharts or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to obtain advice. Note, too, that some elements of the flowchart may not pertain to a particular device, e.g., a software change for an inactive implant; these should be ignored in the application of the model.

Before using the flowcharts, the reader is reminded that specific guidance has been developed for changes to a legally-marketed device that result from a recall. That guidance has been developed separately, but its philosophy is similar to this document in that changes to a device that are intended to bring the device back to its original specifications, and that can be validated under GMPs, do not require a 510(k). On the other hand, changes in specifications that are intended to address the safety or effectiveness problem require a 510(k).[11]

Note that the flowchart entries, "new 510(k)" and "documentation," are written in this way only for conciseness. The reader should interpret "new 510(k)" as **strongly consider submitting a 510(k)** and "documentation" as **document your analysis and file it for future reference.** This is, after all, a guidance document, and it is not intended to be prescriptive. It is intended only to provide the outline of a logic scheme for enhancing the likelihood of good decisions.

Each of the questions listed on the detailed flowcharts are identified by the flowchart letter (A through D) and a sequential number. Those questions on the main spine of the flowcharts relate to major questions to be asked and are identified by a letter and an integer, such as **A1**, **A2**, etc. Subsidiary questions that are asked in response to a "yes" answer are identified by the integer for the question, a decimal point, and a sequential integer, e.g., **C2.1** in Figure 3 labels a decision point containing the question "Is the device an implant?" which follows the determination made in decision point **C2** that a change in material type is contemplated.

Labeling Changes

As noted above, the types of changes are divided into labeling changes, technology or performance specifications changes, and materials changes. All labeling changes are handled with a separate logic scheme that concentrates on changes in indications for use as the threshold for contemplating the submission of a 510(k). Other labeling changes are more frequently recommended for documentation only.

Chart A describes the logic scheme to be used when determining when a 510(k) is required for a labeling change. Changes in device labeling often pose the most difficult questions to be addressed by device manufacturers when deciding whether a new 510(k) submission is necessary. Frequently, an apparently subtle change in a device labeling can have a significant impact on the safe and effective use of the device.

A1 **Does the change affect the indications for use?** The general statement of the "Indications for Use" identifies the target population in a significant portion of which sufficient scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.[12] Changes in the indications for use section of labeling raise more agency concern than any other aspect of labeling. In fact, most changes in this part of the

labeling will require the submission of a 510(k). Any change in the indications for use that limits use to within the currently cleared indication may occur without the submission of a 510(k). For example, the device was cleared for use with three specific indications and the firm decides to market the device for only two of those indications, would not require submission of a new 510(k). Another example would be further limiting the patient population by age or weight e.g., if your device was indicated for use in adults, you could revise the indication to adults 60 years and older but it does not mean you could indicate it for pediatrics. A more difficult case is where the change expands use to closely related populations. In determining whether a change to the indications for use raises issues of safety or effectiveness, the manufacturer should ask whether the change poses any additional risks, expands the use to a new and distinguishable patient population, etc. If the expansion is to a population with similar demographics, diagnosis, prognosis, comorbidity and potential for complications as the original, then a new 510(k) is not ordinarily expected.

Confusion often results when discussing the distinction between "indications for use" and the "intended use" of the device. The regulatory term, "intended use," refers to the objective intent of the persons legally responsible for the labeling of the device. Intent may be determined by written expressions or may be shown by the circumstances surrounding the distribution of the device. The concept of intended use has particular relevance in determining whether a device can be cleared for marketing through the premarket notification (510(k)) process or must be evaluated in a premarket approval application (PMA). Manufacturers should recognize that if a particular labeling change results in a "new" intended use for the device, the agency will find the device to be not substantially equivalent and require premarket approval.

Rather than referring to "intended use" as a determinant in deciding when to submit a 510(k), this guidance identifies several specific labeling changes or modifications that have a major impact on intended use and thus would require the submission of a 510(k).[13] Two common labeling changes that impact intended use and would usually require submission of a 510(k) are:

(1) reuse of devices previously labeled "single use only;" and

(2) changes from prescription to over the counter (OTC).[14]

One exception to (2) above is providing home-use instructions for devices that remain prescription and whose use in the home is accepted medical practice in the United States. Many prescription devices are used in the home with increasing frequency and the Agency believes that 510(k)s are not necessary to add home-use labeling. The reader is referred, however, to the FDA publication, "Write It Right,"[15] for techniques to provide clear and understandable home use instructions.

A2 **Is it a change in warnings or precautions?** In order to facilitate a continuous upgrading in device labeling, manufacturers should monitor device usage and promptly revise the warnings and precautions section based on use experience. Events that precipitate changes of this type are routinely reported under the medical device reporting regulation (MDR) 21 CFR Part 803. 510(k)s for such labeling changes are generally unnecessary however, manufacturer's are encouraged to discuss these situations with CDRH. In any event, manufacturers should always document the basis for these changes in their files.

A3 **Does the change <u>add a contraindication</u>?** While all changes in the labeled contraindications for device use should be reviewed by the agency, CDRH recognizes that, in general, the addition of a contraindication based on new information is important to public health and should be implemented immediately. Because of this, manufacturers are encouraged to add new contraindications to their labeling and to notify existing users of their device as expeditiously as possible whenever a pressing public health need arises. The new labeling should be submitted to FDA as part of a new 510(k) (that is prominently labeled "change being effected"). Manufacturers may continue to market their device with the modified labeling, unless otherwise notified by FDA. Manufacturers should be thoroughly familiar with what constitutes a true contraindication to do this.[16]

A4 **Does the change delete a contraindication?** Deletion of a contraindication usually requires the submission of a 510(k) prior to effecting the change because this type of labeling change typically expands the indications for use. For example, if a physical restraint was contraindicated for use with individuals weighing less than 100 pounds because of established life-threatening and serious adverse events and the manufacturer subsequently wishes to remove this contraindication, a 510(k) should be submitted. Because we recognize that device labeling often includes contraindications that would more appropriately be warnings or precautions, labeling changes that delete contraindications under such circumstances can be made without the need for a 510(k).

A5 **Is the labeling being revised for clarity to insure safer or more effective use?** Device labeling may be changed for a multitude of reasons. Probably, most labeling changes result from attempts to clarify instructions to make the device easier, safer, or more effective to use. In most instances, such labeling changes would not result in the need to submit a 510(k). For example, the instructions for use of an automated clinical chemistry analyzer may be modified to clarify how routine batch testing operation may be temporarily interrupted to allow efficient processing of high priority samples. No 510(k) would be necessary in this instance. However, if the question arises of whether a new 510(k) submission is necessary, manufacturers should document the rationale for their decision.

FDA believes that, if manufacturers follow this approach to changes in device labeling, only necessary 510(k)s (those changes that pose the potential to significantly impact safety and effectiveness) will be submitted while the submission of unnecessary 510(k)s (those where safety and effectiveness are unlikely to be affected) will be minimized. At the same time, manufacturers should be able to retain the flexibility to improve their labeling to insure maximum safe and effective use of their devices.

Technology, Engineering, and Performance Changes

These types of changes encompass a broad span of design activities from minor engineering changes in a circuit board layout to a change from electromechanical to microprocessor control of device function. Chart B illustrates the decision-making logic scheme for such technology, engineering or performance specifications changes to a

device. The key to using this logic scheme is that all changes are evaluated or validated according to the current GMP requirements, and the results of this evaluation/validation are used to guide the decision-making on when to submit a new 510(k).

B1 **Is it a control mechanism change?** Almost all changes in the control mechanism for a device raise questions of safety and effectiveness. Therefore, such changes will normally require the submission of a new 510(k). This is also true for changes in operating principle (decision point **B2**) as well as for changes in energy type (decision point **B3**). (This last was recognized as a significant change both in the statute[17] and the implementing regulations.[18]) Changes of these types tend to be more revolutionary than evolutionary.

One obvious example of a control mechanism change that would raise new questions of safety and effectiveness would be the change from analog to digital control of a medical device. While the change to digital control can markedly improve device performance specifications and effectiveness, the integration of a digital control into a previously all analog system is complex and usually undertaken only as part of a major redesign of a product. Thus, it would be rare that a new 510(k) would not be necessary. Most often, such changes in control mechanism represent the introduction of a new product line.

Other changes in control mechanism of a similar nature would also lead to submission of a new 510(k). An example of such a change would be the change from pneumatic to electronic control of a respiratory care device.

B2 **Is it an operating principle change?** Similar to a control mechanism change, a change in operating principle would also normally lead to the submission of a 510(k). A typical example of a new operating principle for a device would be changing the image reconstruction algorithm used in a computed tomography x-ray system from simple back projection to a new, more radiation-efficient method. In this case, testing both at the bench and in the clinic would be necessary to support a finding of substantial equivalence for the new device.

Such changes may also be accompanied by significant labeling changes and, sometimes, by a need for operator retraining to assure continued safe and effective operation. Note, however, that some minor changes to the algorithm that can easily be validated by the manufacturer may not require the submission of a 510(k). Such incremental software changes are discussed under decision point **B8** below.

B3 **Is it a change in energy type?** Here, too, the submission of a new 510(k) will usually be necessary. For example, changing from AC to battery power is usually part of a redesign to provide a portable device that can be used under different environmental conditions than the original device. Such a change would normally be accompanied by significant labeling changes, including a new or expanded indication for use. Note that this type of change does not include a change from 3V to 9V operation or a change from NICad to lead acid storage batteries. Such changes would be considered changes in performance specifications or technical specifications and are discussed at decision point **B5** below.

B4 **Is it a change in environmental specifications?** See **B8** below.

B5 **Is it a change in performance specifications?** See **B8** below.

B6 **Is it a change in ergonomics of the patient/user interface?** See **B8** below.

B7 **Is it a change in dimensional specifications?** See **B8** below.

B8 **Is it a change in software or firmware?**

The types of changes identified at decision points **B4** through **B8** have frequently been called design changes or engineering changes. They encompass everything from the routine specification changes necessary to maintain or improve device performance as a result of feedback from users,

field or plant personnel, etc., up to and including significant product redesign. The major difficulty lies in sorting out which of these changes is significant enough to trigger the need for a 510(k). The logic scheme that follows is intended to lead a manufacturer through a thought process that will allow routine engineering change orders to occur, while identifying those changes for which a 510(k) would be indicated.

B8.1 **Does the change affect the indications for use?** As with an explicit labeling change, if the change affects the indications for use, i.e., if it creates an implied new indication for use, a new 510(k) should be submitted. An example of this would be changing the length of a surgical scissor from 10 centimeters to 30 centimeters so that the device could be used in laparoscopic procedures. The original indication for use was for open surgical procedures, while the new indication for use would be for closed, endoscopically-controlled procedures. Note that even though a surgical scissor is exempt from the requirement to submit a 510(k) by regulation,[19] one must still evaluate the change to assure that the change does not affect the device's classification or exemption status.[20]

B8.2 **Are clinical data necessary to evaluate safety and effectiveness for purposes of determining substantial equivalence?** Whenever a manufacturer recognizes that clinical data are needed because bench testing or simulations are not sufficient to assess safety and effectiveness and, thus, to establish the substantial equivalence of a new design, a 510(k) should be submitted. In the case of *in vitro* diagnostic devices, however, clinical samples may be collected and analyzed to demonstrate that the device continues to conform to performance specifications as contained in a voluntary standard or as described in a previous 510(k). A new 510(k) is normally not necessary in this situation.

B8.3 **Do results of design validation raise new issues of safety and effectiveness?** All changes to device design will require some level of design validation or evaluation to assure that the device continues to perform as intended. The successful application of routine design validation activities will logically result in manufacturers documenting their efforts and proceeding with the design

change, i.e., assuring that no issues of safety or effectiveness are raised. Occasionally, however, either routine design validation activities produce unexpected results or otherwise prove to be inadequate to validate the design change. In such instances, questions of safety and effectiveness may be associated with the design change, and the manufacturer may need to submit a new 510(k).

For example, a manufacturer sees the need to add a higher kilovoltage position on the control of a conventional diagnostic x-ray system. The results of the design change are predicted based on models, calculations, etc. The new system is used to image a phantom and all results are as predicted. The manufacturer documents the efforts and proceeds to production. On the other hand, a manufacturer of monitoring devices wants to use a more sensitive comparator circuit and makes other design changes to accommodate the more sensitive component. Tests with a simulator produce unexpected results, and additional work is necessary to rationalize what has occurred. The manufacturer should carefully assess what has been done and whether new issues of safety or effectiveness have been uncovered. One key to the answer (but not the only one) is whether a significantly different scheme for design validation was necessary.

B9 **Is there a change in packaging or expiration dating?** Generally, changes in device packaging or changes in the expiration date for use of a device do not result in the need for a new 510(k). Such changes are properly within the scope of GMPs. This is true whether the manufacturer applies an expiration date because of package integrity considerations, e.g., sterility, or because of a finite shelf-life of the device. However, where methods or protocols, not described in the original 510(k), are used to support new package integrity or shelf-life claims, a new 510(k) may be necessary.

B10 **Has there been a change in sterilization?** Changes in sterilization have the potential for affecting the safety or effectiveness of the device and, thus, must be carefully assessed. Changes which have a lower sterility assurance level (SAL) would routinely need a new 510(k) as would those which ordinarily affect the integrity of device materials.

B10.1 Has there been a change in performance specification of the device or in the sterility assurance level attained as a result of the change in sterilization? Changes in the method of sterilization have the potential for changing performance characteristics of a device. This is particularly true of the properties of polymeric materials. When manufacturers make changes in sterilization methods, they must document that the important properties/specifications of the device remain unaffected. In addition, if the SAL is lowered, manufacturers must consider whether device safety or effectiveness may have been compromised by the new level. In general, reductions in SAL should trigger 510(k) submissions unless the SAL remains above 10-6. In any event, manufacturers need to assess critically the need for a new 510(k) for their device in these instances.

Materials Changes

Firms making changes to the materials from which their device is manufactured should first consider the other types of changes discussed above and their impact on the decision regarding the need for a new 510(k). For example, a change of a material type, as discussed below, might also engender a change in the labeling of the device, e.g., the removal of a contraindication or the addition of a new warning, or a change in specifications, e.g., a reduction in the strength of the device. These collateral changes should be considered first, before applying the logic scheme described in this section. See Chart C.

C1 Is the device an in vitro diagnostic product (IVD)? If the device is an IVD, refer to the later section of this Guidance which is specific to materials changes in IVD's (Chart D).

C2 Is this a change in the type of material from which the device is manufactured? Is the generic type of material being changed? There is considerable discussion available regarding what is meant by generic materials types. FDA is developing a Biomaterials Compendium for implant devices which will give form and structure to this discussion. The goal of this Compendium is to relate the type of device to the materials of manufacture. Appendix A to this Guidance is the latest draft of the current tables of generic materials from that Compendium and may be used by manufacturers to help in

their decision-making along with this guidance. Note that even though these tables are not final, they are sufficiently complete to demonstrate the differences in changes in material type and material formulation for most device materials.

C2.1 Is the device an implant? Implant devices are those described in the "permanent contact" category of ISO 10993-1, Section 5.1.4 and 5.2.[21] (Also see the section on "Flowchart Definitions.")

C2.1.1 (Since the device is an implant) Will the material of the affected part of the implant be likely to contact body tissues or fluids? Changes in materials that contact body tissues or fluids may critically affect the device's safety or effectiveness, either because of potentially new interactions of the device material on the body or because of the body's environmental effects on the new material in the device. Manufacturers should submit a new 510(k) for a change in implant material where the material contacts tissue (including bone tissue) or body fluid. Examples of devices for which changes in material type would normally require a new 510(k) are total joints or their components. On the other hand, changes in materials of an implant that are not intended to contact body tissues or fluids are not likely to require a 510(k) submission. Examples of such changes in material type are changes in the interior materials of an implantable electric stimulator (e.g., a single chamber cardiac pacemaker) which are sealed from ingress of body fluids or tissues.

C2.1.2 Is there a change in performance specifications? Frequently, a change in material is made to purposefully alter the performance specifications of a device. In this case, decision point **B5** should be used (in addition to this one) to help decide whether a 510(k) is necessary. Sometimes, however, changes in materials can inadvertently affect the performance of a device. Under GMPs, manufacturers are responsible for assessing whether a change in material affects the device's ability to meet specifications. If performance specifications are inadvertently affected by a materials change, a new 510(k) will probably be necessary. Manufacturers should still use the logic scheme beginning at decision point **B5** to help decide whether a 510(k) should be submitted when performance specifications are inadvertently affected.

C2.2 **Will the material of the affected part of the (non-implant) device be likely to contact body tissues or fluids in vivo?** Non-implant devices include both "limited exposure" and "prolonged exposure" devices, as described in ISO 10993-1: Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing. Examples of prolonged exposure devices that might contact in vivo fluids or tissues are: a parenteral feeding catheter; a wound drain; an infusion catheter; sutures; etc.

C2.2.1 **Considering that the material is likely to contact *in vivo* body tissues or fluids and the requirements of ISO 10993-1, is additional testing required?** ISO 10993-1 outlines a rational process by which a manufacturer can determine which types of biological evaluation should be performed on a device prior to its use with patients. Proper consideration of the various aspects of this evaluation should lead the manufacturer to consistent decisions regarding the changes to the material and the necessity of additional testing. Additional testing is that which would be necessary for a manufacturer to assure that the new material used would not elicit an undesirable patient response. It does not include routine quality assurance testing or verification of the properties of incoming raw materials.

A 510(k) may not be needed if the manufacturer has satisfactory results from the testing indicated by ISO 10993-1 in its files for the material in question or if such results are available to the manufacturer, e.g., are available in the open published literature or have been provided to the 510(k) holder by the material supplier. Applying this principle is much clearer for materials such as metal alloys, where the physical and chemical descriptions for a particular formulation are exact, than it is for materials such as polymers or ceramics, where the characterization of the formulation may be less exact and there may not be a good correspondence between the material formulation intended for use in the device and that formulation for which the results of testing are well established. In this latter instance, additional testing (in the sense of this guidance) is probably necessary.

However, if such additional testing is required, a 510(k) is usually necessary. Note that if testing of the original cleared device was done according to prior FDA guidance (Tripartite Agreement), further testing is necessary only if the manufacturer decides that there are new aspects to the material suggested by ISO 10993-1 that the previous guidance did not suggest.

C2.3 **Is there a change in performance specifications?** Frequently, a change in material is made to purposefully alter the performance specifications of a device. In this case, decision point **B5** should be used (in addition to this one) to help decide whether a 510(k) is necessary. Sometimes, however, changes in materials can inadvertently affect the performance of a device. Under GMPs, manufacturers are responsible for assessing this possibility. If performance specifications are inadvertently changed, it is possible that a new 510(k) is necessary. Manufacturers should still use the logic scheme beginning at decision point **B5** to help decide whether a 510(k) is necessary.

C3 **Is this a change in the formulation of the material, but not a change in material type?** These are changes within a single generic material type that can affect the chemistry, metallurgy, or other property or stability of the material. These do not include changes in processing aids, catalysts, residual contaminants, or manufacturing aids that are not intended to be part of the material. An example of a change in material formulation is a change from one type of polyurethane to another or a change from a AISI Type 316 stainless steel to a AISI type 400 stainless steel. To determine the need for a 510(k) for a change in material formulation, the same logic used for a change in material type should be followed. (See **C2.1** above.) Note that there is no "Generally-Recognized-as-Safe" list of implant materials. Even though a material may work well as an implant in one part of the body, there is no assurance that it will perform as well in another.

C4 **Is there a change in the vendor of the raw material from which the device is manufactured?** Changes in the suppliers of raw materials to the manufacturers of medical devices are described in both the existing GMP regulations[22] and 510(k) regulations.[23] These regulations establish the responsibility of the device manufacturer to purchase those materials against a materials specification. Such a specification would require particular performance characteristics of the raw materials related to the desired performance of the finished device. The controlling aspect of the logic scheme for this change is the existence of such a material specification.

C4.1 **Is the new material being supplied to a specification?** If the material is being supplied to the device manufacturer's specification, a 510(k) is probably not necessary. For example, a device manufacturer might include a transparency requirement in the purchase specification for tubing to be used in an implantable catheter. Such a requirement might be related to the later processing of the tubing into the finished device. To change the supplier of that material without the need for a new 510(k), the specification should include a transparency requirement, and the device manufacturer's design validation, as required by the GMP regulation, must describe the rationale for that transparency requirement. Further, the manufacturer should document that component specifications are still met and that the performance specifications (characteristics) of the device are not adversely affected.

Materials Changes for *In vitro* Diagnostic Products

D.1 **Is there a change in performance specifications?** Changes in the material used in an IVD can affect the performance of the device and should be assessed as to their impact on safety and effectiveness.

D.1.1 **Does the change in the performance specifications of the IVD mean that new clinical data (clinical samples) will be necessary to establish the safety and effectiveness of the device for the purpose of demonstrating substantial equivalence?** An example of a change where a new 510(k) would be required is when the material change results in a change in the cut-off. In that case, clinical testing would be required, and the results should be part of the new 510(k). (Note that clinical testing for an IVD refers to testing of clinical samples either at the manufacturing site or at sites of intended use.) An example where new clinical data are necessary, but a new 510(k) is not necessary, is when no labeling changes would be made because comparison of the changed device with the legally marketed device demonstrates statistically equivalent performance.

D.1.2 **Does the change in the performance specifications of the IVD mean that new clinical data will be necessary to show continuing conformance of the device to a recognized standard?** Voluntary standards such as those developed by the National Committee of Clinical Laboratory Standards (NCCLS), the National Cholesterol Educational Program and other professional

groups may be part of the basis of a substantial equivalence determination for an IVD. Deviation of IVD performance specifications from the performance values of widely accepted voluntary standards should always be communicated to potential users. Such deviations may also indicate that substantial equivalence of the device is in question, and a 510(k) should be submitted.

D.1.3 Do the results of the design validation performed as a result of this change in materials raise new issues of safety and effectiveness? As noted above, design validation is required when changes are made to any device, including an IVD. If the results of such validation raise new issues of safety or effectiveness, thus indicating that the performance of the device is not known or well established, a new 510(k) may be necessary. This might be the case, for example, if standard methods of design validation for IVDs are not possible and non-standard methods must be applied.

D.2 Does the change in material alter the operating principle of the IVD? Examples of changes in materials that alter the operating principle of the device and would routinely require a 510(k) are: changes from liquid to solid reagent; change from an RIA to a non-RIA; changes in the source and type of an antibody, likely to produce a change in antibody specificity, affinity, or purity; change from immunofluorescence to ELISA; or a change in conjugates. Examples of changes that might affect the operating principle of the IVD are changes in reaction components or materials such as calibration materials and quality control materials or changes in methods such as specimen pretreatment, incubation times and temperatures. If these changes produce statistically significant deviations in device performance that result in modified reporting of performance in labeling, they would require a new 510(k). If no statistically significant deviations are observed and labeling is not changed, a new 510(k) submission would not be necessary. Examples of changes in materials which do not ordinarily affect the operating principle are changes in preservatives and changes in formulations of the existing materials.

Definitions

The following definitions are provided to clarify the meaning of terms used in the flow chart. Wherever possible, existing definitions from the Food, Drug, and Cosmetic Act, the medical device regulations, or ODE Bluebook memoranda have been used. In some cases, where regulatory definitions are unavailable, we have relied on strict dictionary definitions of terms.

Change: As used in the model, this means a proposed change and not the impact of a proposed change. Important impacts of a proposed change are identified on the flow chart. For example, a manufacturer may propose a change in method of sterilization. This change could impact on performance specifications because of potential chemical or physical damage to the device. The proposed change (in method of sterilization) is the change that should be used in the model.

Contraindications: See "precautions, warnings and contraindications" below.

Control Mechanism: The manner by which the actions of a device are directed. An example of a change in control mechanism would be the replacement of an electro-mechanical control with a microprocessor control.

Dimensional Specifications: The physical size and shape of the device. Such specifications may include the length, width, thickness, or diameter of a device, as well as the location of a part or component of the device.

Documentation: For the purpose of this guidance, documentation means recording the results of applying the model to proposed changes in a device. Consideration of each decision point should be recorded, as well as the final conclusions reached. If testing or other engineering analysis is part of the process, the results of this activity should be recorded or referenced. A copy of this documentation should be maintained for future reference.

Energy Type or Character: The type of power input to or output from the device. Examples of a change in energy type or character would be a change from AC to battery power (input) or a change from ionizing radiation to ultrasound to measure a property of the body (output).

Environmental Specifications: The (range of) acceptable levels of environmental parameters or operating conditions under which the device will perform safely and effectively. Examples of changes in environmental specifications are expanding the acceptable temperature range in which the device will operate properly or hardening the device to significantly higher levels of electromagnetic interference.

Ergonomics of Patient/User Interface: The way in which the device and the patient/user are intended to interact. Examples of this would be the various audible or visible alarms intended to alert the user to a hazardous condition, the layout of a control panel, or the mode of presentation of information to the user.

Expiration date: The date beyond which there are no data to assure that the product may perform safely or effectively and beyond which the manufacturer states the product should not be used.

Implant: A device that is intended to reside within a surgically or naturally formed channel or cavity of the human body for a period of more than 30 days (excluding dental restoration materials).

Intended Use: Intended use refers to "the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article ...."[24]

Indications for use: An indication for use is "a general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."[25] The indications include all the labeled patient uses of the device, for example:

- the condition(s) or disease(s) to be screened, monitored, treated, or diagnosed,
- prescription versus over-the-counter use,
- part of the body or type of tissue applied to or interacted with,
- frequency of use,
- physiological purpose (e.g., removes water from blood, transports blood, etc.), or
- patient population.

The indications for use are normally found in the indications section of the labeling, but indications may also be inferred from other parts of the labeling such as the precautions, warnings, or the bibliography sections. In some instances, a change in the indications for use may be a new intended use for the device, in which case, the 510(k) for the changed device would be found not substantially equivalent and a premarket approval application or a reclassification petition would be necessary.[26]

In vitro Device: Those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.[27]

Label: The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article.[28]

Labeling: The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or its containers or wrappers, or (2) accompanying such article.[29] This can include, among other things, any user or maintenance manuals and, in some instances, promotional literature.

Manufacturer: For the purposes of this document, the term manufacturer includes any 510(k) holder, even if that person does not actually fabricate the existing device. The term also includes persons who have a preamendments device or a device that is currently exempt by regulation from the 510(k) requirements of the act.

Material Formulation: The base polymer formulation or the alloy, additives, colors, etc., used to establish a property or the stability of the material. This does not include processing aids, mold release agents, residual contaminants, or other manufacturing aids that are not intended to be a part of the material. An example of a change in material formulation would be a change from a series 300 stainless steel to a series 400 stainless steel.

Material Supplier: The firm supplying the raw material to a finished device manufacturer.

Material Type: The generic name of the material from which the device is manufactured. (Use the generic name in the biomaterials compendium.) An example of a material type change would be the change from natural latex rubber to synthetic rubber.

Method of Sterilization: The physical or chemical mechanism used to achieve sterility or to achieve a specific sterility assurance level (SAL).

Operating Principle: The mode of operation or mechanism of action through which a device fulfills (or achieves) its intended use. An example of a change in operating principle would be using a new algorithm to compress images in a picture archiving and communications system. For an IVD, an example would be a change from immunofluorescence to ELISA.

Packaging: Any wrapping, containers, etc., used to protect, to preserve the sterility of, or to group medical devices.

Performance Specifications: The performance characteristics of a device as listed in device labeling or in finished product release specifications. Some examples of performance specifications are measurement accuracy, output accuracy, energy output level, and stability criteria.

Preamendments Device: A device legally marketed in the United States prior to May 28, 1976.

Precautions, Warnings, and Contraindications:

- Precautions describe any special care to be exercised by a practitioner or patient for the safe and effective use of a device. This definition also include limitations stated for IVDs.

- Warnings describe serious adverse reactions and potential safety hazards that can occur in the proper use or misuse of a device, along with consequent limitations in use and mitigating steps to take if they occur.

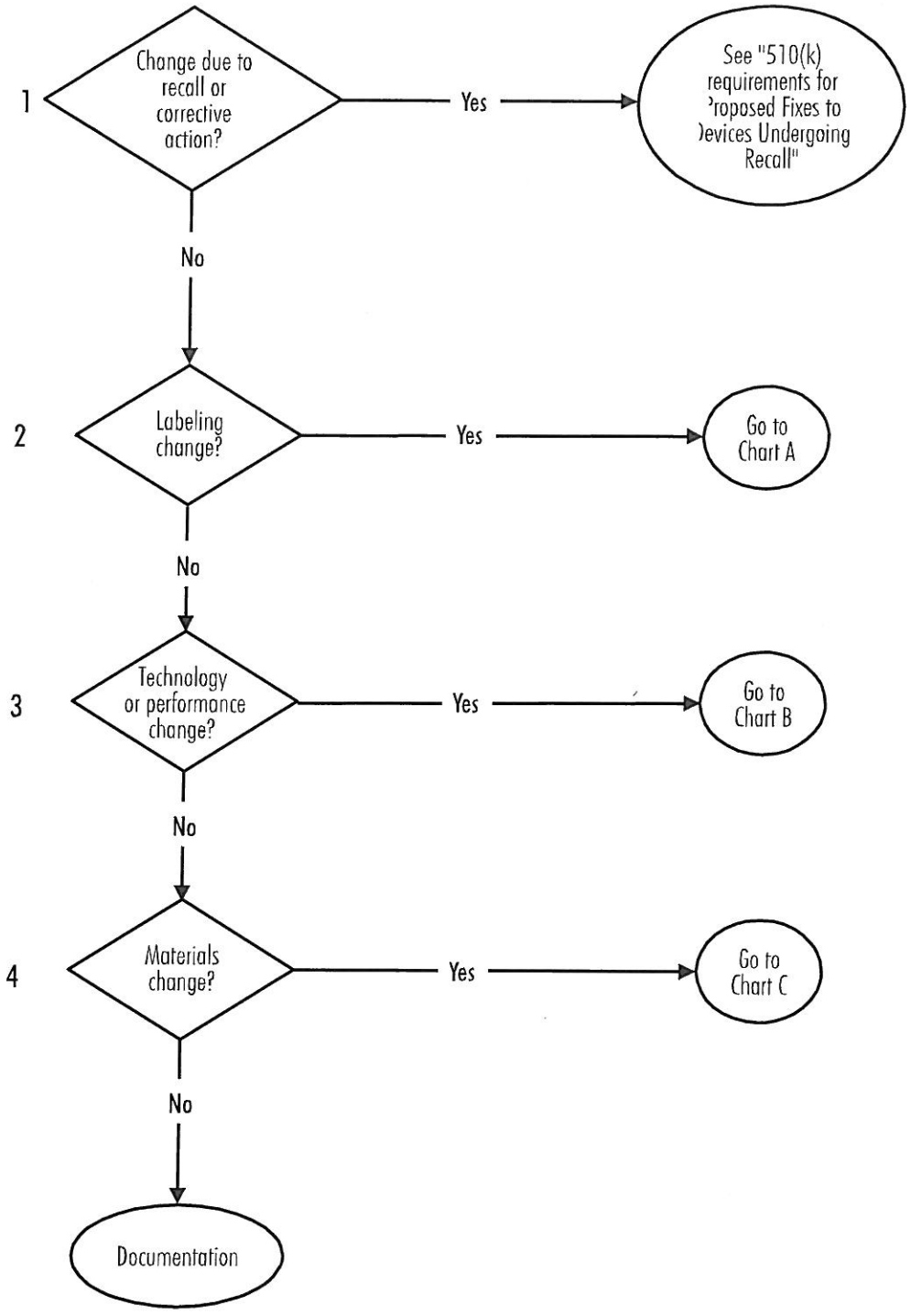
- Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any reasonably foreseeable benefits.[30]

Reuse: Use of a device more than once on a single patient or on more than one patient. Actions necessary for reuse of a device may include instructions for assembly/disassembly, on-site sterilization or disinfection, etc. This definition does not include the refurbishing or repair of a device for redistribution or resale.

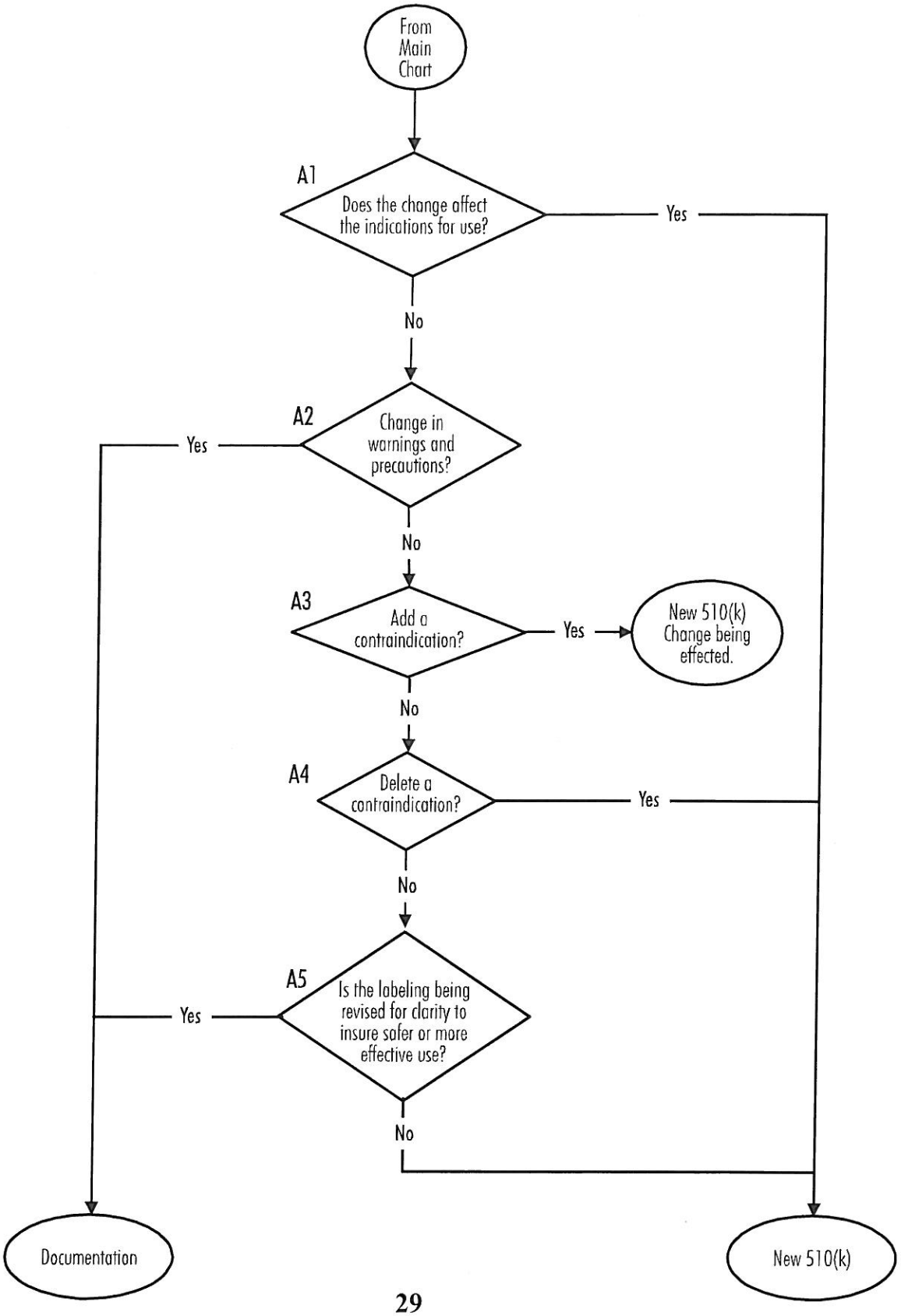
Software: The set of instructions used to control the actions or output of a medical device, to provide input to or output from a medical device, or to provide the actions of a medical device. This definition includes software that is imbedded or permanently a part of a medical device, software that is an accessory to a medical device, or software that is itself a medical device.

Warnings: See "precautions, warnings, and contraindications" above.

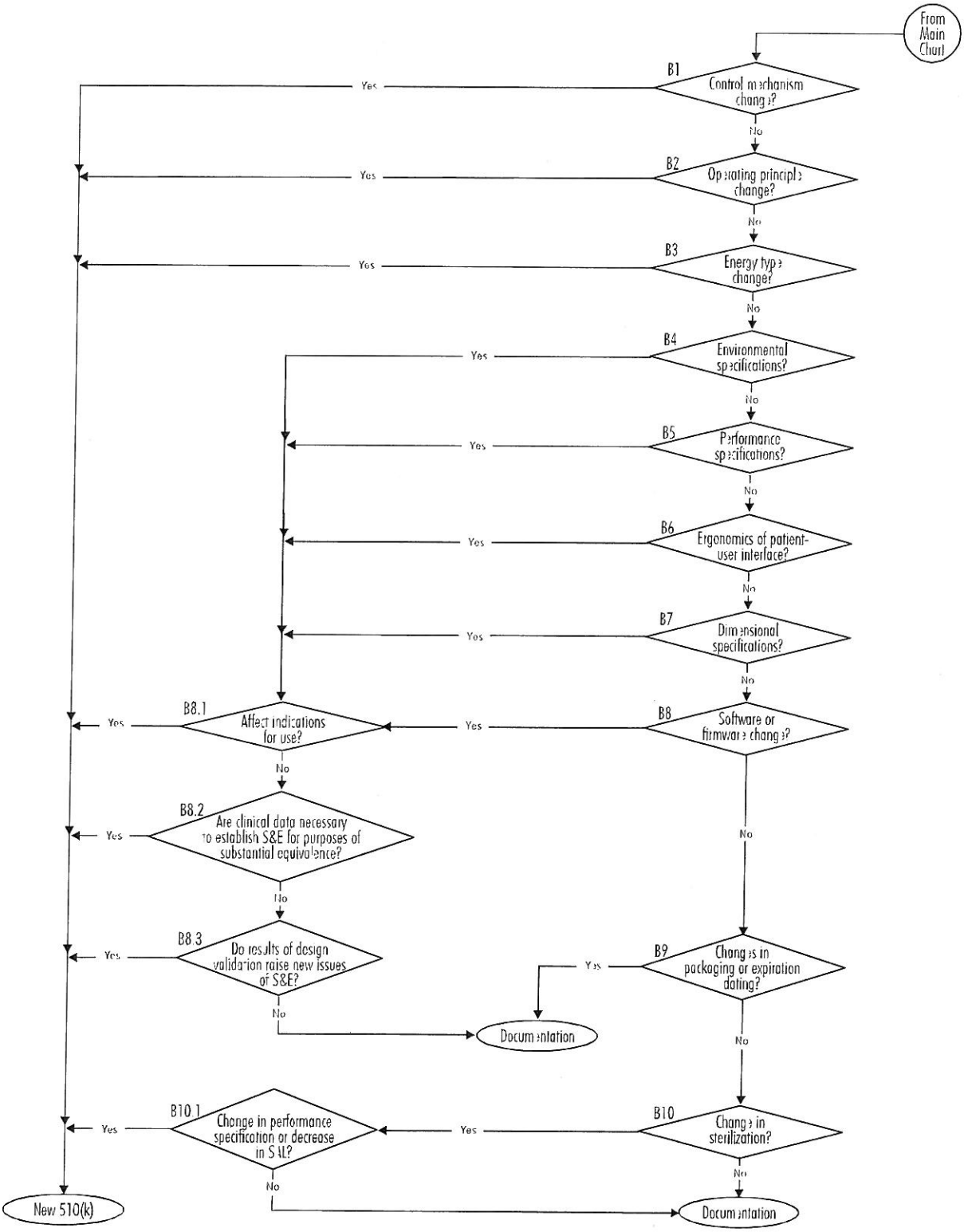
MAIN FLOWCHART
WHEN TO FILE A 510(k) AFTER CHANGE TO A LEGALLY MARKETED DEVICE



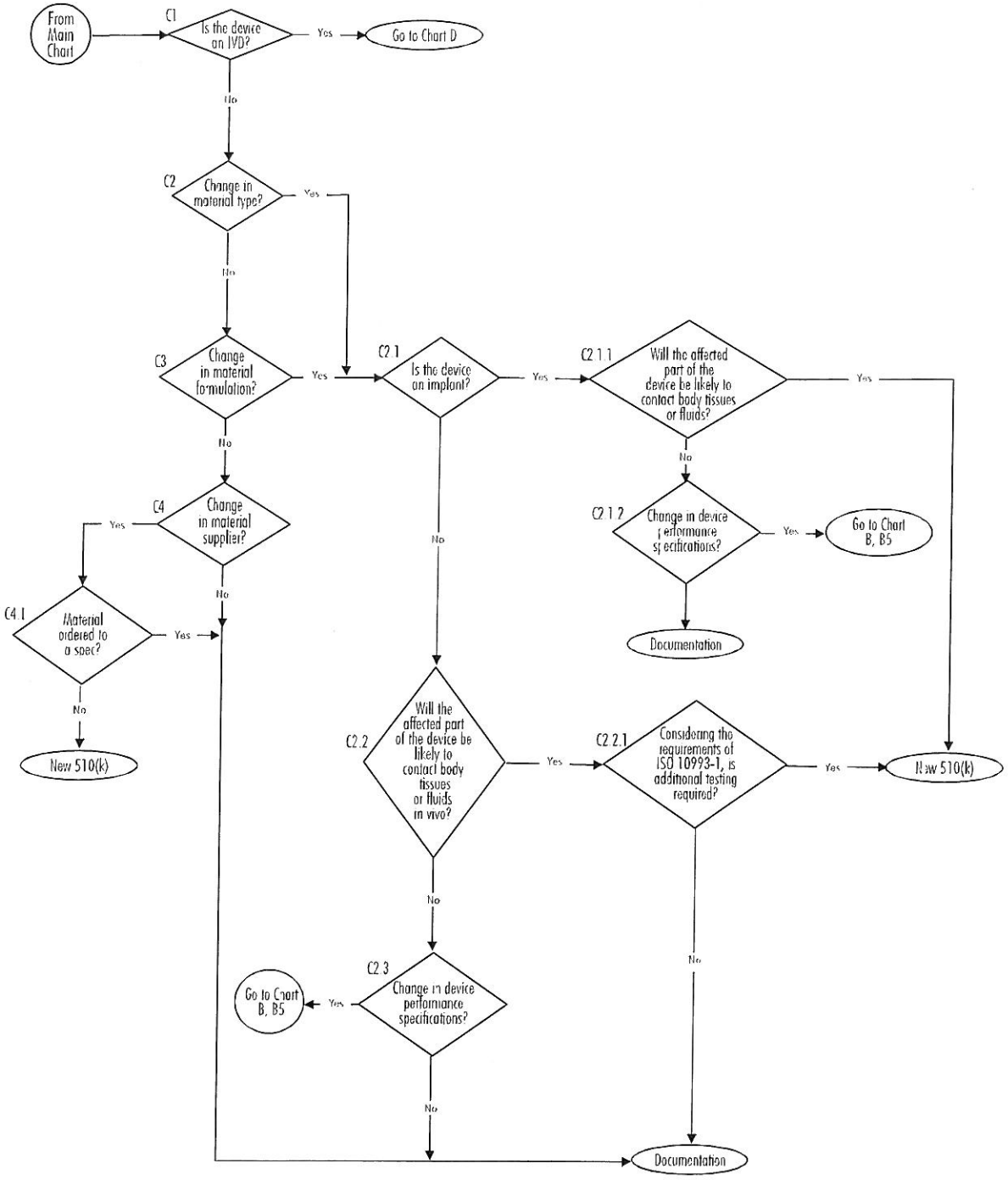
FLOWCHART A - IS IT A LABELING CHANGE?



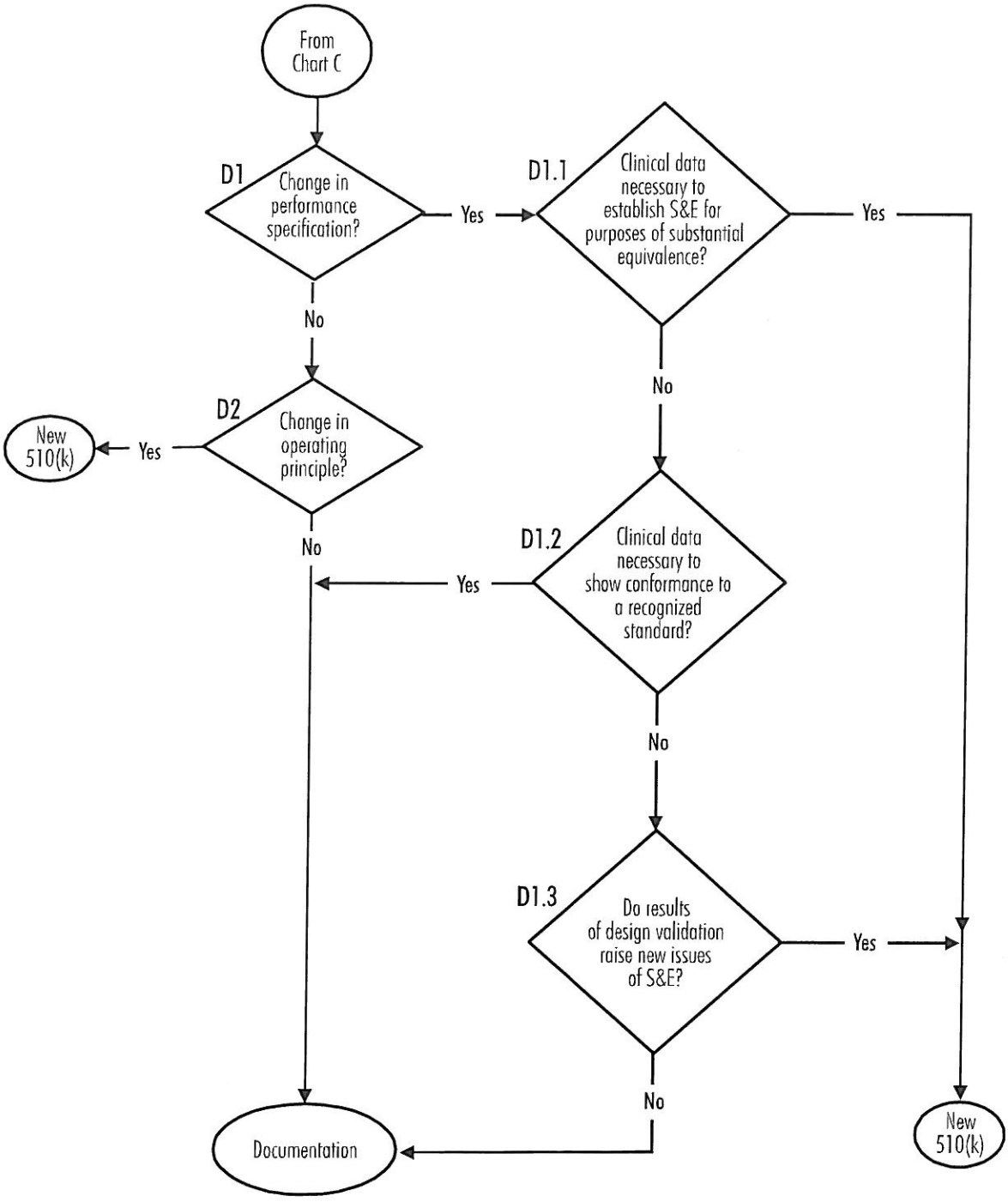
FLOWCHART B - IS IT A TECHNOLOGY OR PERFORMANCE CHANGE?



FLOWCHART C - IS IT A MATERIALS CHANGE?



FLOWCHART D - MATERIALS CHANGE FOR AN IVD



APPENDIX: DRAFT CONTROLLED VOCABULARY FROM THE FDA BIOMATERIALS COMPENDIUM

Material Class

metals
polymers
ceramics
composites
biological origin

Material Subclasses

Metals	Polymers	Ceramics
stainless steel	thermoplastics	Al compound
Co & Ni allay	thermoset/elastomers	Ti compound
tantalum alloy	absorbable	Zr compound
titanium alloy	adhesive	Ca compound
zirconium alloy	fluids	carbon
precious/noble		glass
amalgam		
miscellaneous		

Composites	Biologic Origin
polymer matrix	tissues
metal matrix	cells
ceramic matrix	biomolecules
	antimicrobials

METALS

Generic Material Names

Stainless Steels	Co & Ni Alloys	Ti Alloys
316L FeCrNiMo	CoCrMo period	CpTi (grade 1-4)
nitrogen strengthened	CoCrWNi	Ti 6Al 4V
ferritic	CoNiCrMo	Ti 6Al 7Nb
martensitic	CoNiCrMoWFe	Ti 5Al 2.5 Fe
austenitic	CoCrNiMoFe	Ti 3.8Al15Mo5Zr
	Nickel based	Ti 13Nbl3Zr
		Ti 12Mo6Zr2Fe
		Ti 15Mo2.8Nb.2Si
		NiTi alloy

Zr Alloys	Ta Alloys	Precious/Noble
Zr2.5Nb	unalloyed Ta	gold
		silver
Amalgams	**Miscellaneous**	platinum
Ag-Hg	aluminum	palladium
Cu-Sn	copper	iridium
	mercury	Pt/Ir

POLYMERIC MATERIALS

Thermoplastics	Thermoset/Elastomer	Absorbable
acetal (POM)	bis/GMA	polyester
acrylic (hydrogels)	butyl	polyether
acrylic (MMA,PMMA)	epoxy	polyanhydride
fluorocarbon	EPDM rubber	polyorthoester
parylene	hydrogel based	polyetheramide
PEO hydrogel	natural latex	
poly(aryl)ether ketone	polyesterurethane	
poly(aryl)sulfone	polyetherurethane	
polyethersulfone	polyurethane (other)	
polyamide (nylon)	polyether	
polycarbonate (PC)	polyisoprene	
polyesters (PET, PBT)	polysulfide rubber	
polyester copolymer	rubber-modified acrylic	
polyethylene (PE)	silicone gel	
polyethylene (UHMWPE)	silicone elastomer	
polyimide		
polypropylene (PP)		
polystyrene (PS)		
polyurethane (PU)		
polyvinyl alcohol (PVO)		
polyvinyl chloride (PVC)		
polyvinylidine chloride		

Adhesives	Fluids
acrylic based	polyvinylpyrrolidone
cyanocrylate	silicone (PDMS)
epoxy	
polyurethane	
silicone	
UV curable	

CERAMICS and COMPOSITES

CERAMICS

Al Compounds	Ti Compounds	Zr Compounds	Ca Compounds
alumina	TiN	CaO stabilized	Beta-TCP
ruby	titanium carbide	MG-PSZ	calcium phosphate
sapphire	titanium dioxide	Y-TZP	calcium hydroxyphosphate
		zirconium dioxide	calcium sulfate
			calcium aluminate
			gypsum
Carbon	**Glass**		HA/TCP
fibers	bioactive glass		hydroxylapatite
graphite	silica based		
LTI pyrolytic			
LTI-Si alloy			
ULTI pyrolytic			
vapor deposited			
vitreous			

COMPOSITES

Polymer Matrix	Metal Matrix	Ceramic Matrix
acrylic glass	Ag-MP35 I?	Calcium hydroxide
bis/GMA composites	Ta-Elgiloy wire	carbon-carbon
ceramic particle reinforced		glass ionomer cement
CFR epoxy		porcelain
CFR poly(etherketones)		silicate cement
CFR poly(imide)		zinc oxide eugenol
CFR Poly(sulfone)		zinc phosphate cement
CFR UHMWPE		zinc polycarboxylate cement
glass reinforced		
metal fiber reinforced		
PTFE composite		
PU/PC		
urethanedimethacrylate		

BIOLOGICAL ORIGIN

Tissues	Cells	Biomolecules	Antimicrobials
blood vessel	adipocyte	agar	aminoglycoside
bone	bone marrow	albumin	anti-fungal
cartilage	chondrocyte	alginate	anti-mycobacterial
coral	endothelial	BMP	cephalosporin
cornea	epithelial	cellulose	penicillin
dura mater	fibroblast	chitosan/chitan	polymyxin
fascia lata	hepacyte	collagen	quinolone
fibrous sheath	islet	elastin	sulfonamide
heart valve	keratinocyte	fibrin	tetracycline
joint	osteoblast	fibrinogen	vancomycin
ligament/tendon	renal tubular prog.	fibronectin	
pericardium	smooth muscle	gelatin	
umbilical cord		growth hormones	
umbilical vein		heparin	
viscera		hyaluronic acid	
		hydroxypropylmethylc ellulose	
		insulin	
		molluscan glue	
		PHB	
		phospholipids	
		polyaminoacids	
		protein extract	
		RDG protein	
		saline	
		silk	
		triglicerides, soybean oil	

References

[1] 21 CFR 807.81(a)(3).

[2] Section 520(f) of the Food, Drug, and Cosmetic Act.

[3] 61 FR 52501-52662, October 7, 1996.

[4] Section 704(e) of the Food, Drug, and Cosmetic Act.

[5] ODE Bluebook Memorandum No. K86-3 (June 30, 1986), " Guidance of the CDRH Premarket Notification Review Program."

[6] 21 CFR 820.3(w), effective June 1, 1997.

[7] See, for example, ODE Bluebook Memoranda K86-3, K90-1, etc. As well as device specific guidance documents.

[8] 21 CFR 807.92(a)(3).

[9] "Premarket Notification Document (510(k)) for Daily Wear Contact Lenses," May 12, 1994.

[10] 21 CFR Part 820

[11] ODE Bluebook Memorandum K95-1 (November 21, 1995), "510(k) Requirements During Firm-Initiated Recalls."

[12] ODE Bluebook Memorandum G91-1 (March 8, 1991), "Device labeling guidance."

[13] 21 CFR 807.81(a)(3).

[14] 21 CFR 801 Subparts C and D.

[15] "Write It Right, Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care," HHS Publication (FDA) 93-4258, August 1993.

[16] ODE Bluebook Memorandum G91-1 (March 8, 1991), "Device Labeling Guidance."

[17] Section 513(i)(1) of the Food, Drug, and Cosmetic Act.

[18] 21 CFR 807.81(a)(3).

[19] 21 CFR 878.4800.

[20] 21 CFR 878.9 "Limitations of exemptions from section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act)."

[21] ISO 10993-1, Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing.

[22] 21 CFR 820.80(a).

[23] 21 CFR 807.81(a)(3)(i).

[24] 21 CFR 801.4 "Meaning of intended uses."

[25] 21 CFR 814.20(b)(3)(i).

[26] ODE Bluebook Memorandum K86-3 (June 30, 1986), "Guidance on the CDRH Premarket Notification Review Program."

[27] 21 CFR 809.3(a).

[28] Section 201(k) of the Food, Drug, and Cosmetic Act.

[29] Section 201(m) of the Food, Drug, and Cosmetic Act.

Appendix VI

2011 Draft 510(k) Device Modifications Guidance (withdrawn)

Page 83

Guidance for Industry and FDA Staff

510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: July 27, 2011

On July 28, 2011 this document was edited to correct a typo on P.5.

For questions regarding the use or interpretation of this guidance in the review of submissions to the Center for Devices and Radiological Health, contact Michael J. Ryan at 301-796-6283 or by email at michael.ryan@fda.hhs.gov.

For questions regarding the use or interpretation of this guidance in the review of submissions to the Center for Biologics Evaluation and Research, contact the Office of Communication, Outreach and Development at 1-800-335-4709 or 301-827-1800 or by email at ocod@fda.hhs.gov.

When final, this document will supersede *Deciding When to Submit a 510(k) for a Change to an Existing Device*, dated January 10, 1997.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

Public Comment

Written comments and suggestions may be submitted at any time for FDA (Agency) consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, refer to Docket No. FDA-2011-D-0453. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 240-276-3151 to receive a hard copy. Use the document number (1793) to identify the guidance you are requesting.

Or, contact:

Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Internet:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm
Tel: 800-835-4709 or 301-827-1800
E-mail: ocod@fda.hhs.gov

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

21 CFR 807.81(a)(3) 2
Changes that "Could Significantly Affect" Safety or Effectiveness 2
"A Major Change or Modification in the Intended Use" of a Device 3

III. SCOPE 3

IV. BASIC PRINCIPLES 4

Important Note on 510(k) Devices that Contain Nanomaterials or Otherwise Involve the Application of Nanotechnology: 7

V. MANUFACTURING PROCESS CHANGES 7

VI. LABELING CHANGES 9

VII. TECHNOLOGY, ENGINEERING, AND PERFORMANCE CHANGES 12

VIII. MATERIALS CHANGES 22

IX. IS CLINICAL DATA NECESSARY TO DETERMINE SUBSTANTIAL EQUIVALENCE? 23

Guidance for Industry and FDA Staff

510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

FDA developed this draft document to provide guidance to manufacturers on when to submit a premarket notification submission (510(k)) for changes or modifications made to that manufacturer's[1] previously cleared medical device. The underlying principles that FDA uses to determine when a 510(k) is necessary for a modified device are explained here, and examples are provided for additional clarity. When final, this guidance will supersede the 1997 version of the guidance document, *Deciding When to Submit a 510(k) for a Change to an Existing Device*.

In 2010, FDA initiated a review of its process for premarket review of medical devices and undertook two significant initiatives to improve the Agency's medical device premarket review programs. In August 2010, FDA released two reports, including the analyses and recommendations that suggested changes were needed to improve the predictability, consistency, and transparency of these programs. After receiving input from industry, stakeholders and the public, in January 2011, FDA announced 25 specific actions that the Agency will take to improve the premarket review programs. Updating the 1997 version of the guidance document, *Deciding When to Submit a 510(k) for a Change to an Existing Device,* is one of these actions.

The recommendations in this draft guidance document are consistent with FDA policy for when a modification to a device does – and does not – require the submission of a 510(k).

[1] For the purposes of this document, the term "manufacturer" includes any 510(k) holder, even if that person does not actually fabricate the existing device. The term also includes persons who market a preamendments device (a device legally marketed in the US prior to May 28, 1976) or a device that is currently exempt from the 510(k) requirements of the FD&C Act.

The guidance has been updated, however, to address issues associated with software and other rapidly changing technologies, and to provide greater clarity about changes that do not trigger the need for a new premarket submission. This guidance uses examples of modifications to devices involving such technologies to illustrate changes that require a new 510(k), and changes that may simply be documented in accordance with a manufacturer's existing Quality System without prompting the need for a new 510(k) submission. FDA believes increased certainty about the regulatory consequences of device modifications is critical to facilitating advancements in device technology.

FDA's guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidance documents means that something is suggested or recommended, but not required.

II. Background

21 CFR 807.81(a)(3)

Almost from the 1976 enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (the FD&C Act), FDA has attempted to define with greater clarity when a modification to an existing medical device would – or would not – trigger the requirement that a new 510(k) be submitted to the Agency and cleared prior to marketing of the modified device. FDA regulations (21 CFR 807.81(a)(3)) state that a 510(k) must be submitted when:

> (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 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.

FDA issued the original guidance document *Deciding When to Submit a 510(k) for a Change to an Existing 510(k)* in 1997 to clarify the language used in this regulation, particularly the phrase "could significantly affect the safety or effectiveness" and use of the adjectives "major" and "significant." Since then, regulatory changes such as the implementation of the Quality System regulation (21 CFR part 820) have occurred, and medical device technology has evolved. Accordingly, FDA is issuing this draft, updated guidance to reflect the Agency's current thinking and emphasize the most important factors in determining whether to submit a 510(k) for a device modification.

Changes that "Could Significantly Affect" Safety or Effectiveness

The regulation, 21 CFR 807.81(a)(3), requires a new 510(k) for any change or modification that "could significantly affect" either the safety or the effectiveness of a device. Whether a change could *significantly* affect the safety or effectiveness of a device is the key issue this guidance tries to address. It is important to note that device changes intended as improvements to a device's safety or effectiveness could significantly affect the safety or effectiveness and require a new 510(k).

It is also important to note that the question addressed by this guidance is a different question from whether a change *does* significantly affect the safety or effectiveness of a device. Whether a change *does* affect safety and effectiveness is typically demonstrated by testing submitted in a 510(k) application. In most cases testing cannot, however, conclusively show that a change could not affect safety or effectiveness. We have developed this draft guidance to categorize the types of changes likely to require new 510(k) submissions, the types of changes that generally do not require new submissions, and to identify gray areas where we recommend sponsors speak to the agency before determining whether a new 510(k) should be submitted.

"A Major Change or Modification in the Intended Use" of a Device

Section 513(i) of the FD&C Act provides that a device may only be found substantially equivalent to a legally marketed predicate device if, among other things, the device has the same intended use as the predicate device. Thus, if a device modification results in a new intended use for the device, the Agency must find the device to be not substantially equivalent (NSE) and the device will require premarket approval. Changes to the indications for use, however, do not necessarily constitute a new intended use that would render the device NSE and trigger the requirement for a PMA. However, because changes to the indications for use are generally "major" changes to the intended use under 807.81(a)(3), they generally will require submission of a new 510(k). To clarify this principle, this guidance identifies several specific labeling changes or device modifications that affect the indications for use in a way that they have a major impact on intended use and thus require the submission of a 510(k).

III. Scope

This guidance applies to devices that are subject to premarket notification requirements. This guidance does not address issues unique to combination products, although the principles discussed in this guidance may be applied to submissions for combination products on a case-by-case basis. Contact the Office of Combination Products (OCP) for information on combination products at 301-796-8930 or combination@fda.gov. Furthermore, this guidance is not intended to address the need for submitting 510(k)s by remanufacturers[2] of devices for which they do not hold the 510(k).[3]

---

[2] 21 CFR 820.3(w): "*Remanufacturer* means 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."

[3] See, for example, *Guidance for Industry and FDA Reviewers - Reprocessing and Reuse of Single-Use Devices* and *Frequently-Asked-Questions about the Reprocessing and Reuse of Single-Use Devices by Third-Party and Hospital Reprocessors*

The types of modifications addressed in this draft guidance include manufacturing process changes, labeling changes, technology or performance specification changes, and materials changes. This guidance is intended to assist industry in determining whether a new 510(k) is submission is necessary whenever a manufacturer makes a change to its own legally marketed device. This guidance may be used to determine whether device modifications made as corrective actions in recall situations warrant a new 510(k) submission. (See the Blue Book Memorandum K95-1, *510(k) Requirements During Firm-Initiated Recalls*; if a correction alters a device rather than simply restoring it to its original specifications, a new 510(k) may be necessary. This guidance may be useful in determining whether one is warranted in cases where the correction does alter the device.)

This draft guidance document incorporates existing guidance and policy[4] regarding when 510(k)s are necessary for modifications to legally marketed devices. In some cases, the existing guidance derives from advice given to only a few manufacturers for a limited number of devices. In such instances, we have attempted to generalize the concepts to apply to a broader range of devices. However, special cases exist where both manufacturers and FDA have worked to establish guidance for modifications to specific devices, e.g., daily wear contact lenses (see *Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses*). This draft guidance is not intended to supplant such existing device-specific guidance but may cover areas not addressed in those device-specific guidances. This draft guidance is also not meant to supersede the Office of In Vitro Diagnostic Device Evaluation and Safety's (OIVD) *Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy*.

The questions and answers in the following sections are provided as guidance to help manufacturers in determining whether a new 510(k) is necessary for a change or modification to an existing device. Manufacturers make the initial determination of whether a device modification requires a new 510(k), while FDA staff may review these decisions during post-market inspections. These questions should not be considered to be all-inclusive, as it is not possible for a single document to cover all possible device changes. The question and answer sections cover the following types of changes:

- Manufacturing changes
- Labeling changes
- Technology or performance specification changes
- Materials changes

IV. Basic Principles

Certain principles of section 807.81(a)(3) affect the need to submit a 510(k) for a change to an existing device. The following basic principles underlie this guidance document:

[4] See, for example, ODE Bluebook Memoranda K86-3, K90-1, etc., as well as device-specific guidance documents.

- Any person who is required to register under section 510 of the FD&C Act and 21 CFR 807.20 who plans to market a device for the first time (i.e., one that is not a modified version of a manufacturer's own already cleared device) is required to submit a 510(k).

- This draft guidance does not address medical devices that are exempt from 510(k) requirements under sections 510(l) or (m) of the FD&C Act. Changes to devices that are exempt from 510(k) requirements under those sections do not require 510(k) submissions unless the modified device exceeds the limitations of exemption described in section .9 of 21 CFR Parts 862-892 (i.e., 21 CFR 862.9, 21 CFR 864.9, etc.).[5]

- To determine whether a device modification is significant and thus requires a new 510(k), a manufacturer should compare the modified device to the most recently cleared version of that device and decide whether the modification could significantly affect the safety or effectiveness of the device. It follows from this basic principle that a number of comparisons are not relevant to the decision about submitting a new 510(k):

    - The modified device should not be compared to multiple devices, only to the most recently cleared version of that device, as described in that 510(k) submission.[6]
    - The modified device should not be compared to a version of the device that has not received clearance. In cases where a manufacturer has made several modifications to a device and judged that they do not require submission of a new 510(k), the modified device should be compared to the most recent version of the device that received 510(k) clearance, as it was described in that 510(k) submission.
    - The modified device should not be compared to any other device produced by the same manufacturer or another manufacturer, even if the other device could serve as a predicate to the modified device. The decision whether to submit a new 510(k) for a modified device is not based on whether the modified device is substantially equivalent to another device, it is based on whether the modification could significantly affect safety or effectiveness or whether it is a major change in the intended use of the device.

      For example: A manufacturer produces two legally marketed devices; Device A has design A and is made of material A, Device B has design B and is made of material B. If the manufacturer modifies Device A to be made of material B, it would be inappropriate to assume that because material B is part of a different 510(k)-cleared device the modification does not require a new 510(k). It would also be inappropriate to compare the modified Device A with material B to any other legally marketed device to decide whether a new 510(k) is necessary, even if the other marketed device would be an obvious predicate device for purposes of determining substantial equivalence of the modified device.

---

[5] FDA's regulations also contain exemptions from premarket notification requirements in 21 CFR 807.85. No premarket submissions is required for a device modification that falls within these exemptions.

[6] Cleared 510(k) premarket notifications are listed in FDA's *510(k) database*.

- A manufacturer should answer the questions posed below, in Sections V-IX, for *each individual change* to its device until a decision is made either to submit a 510(k) or to document the change and the basis for concluding that it does not require a 510(k). For instance, if a manufacturer changes the length of a device, the thickness of the device, and the material of the device, each of these three changes should be considered individually.

- Individual changes that do not require a new 510(k) may require one when evaluated collectively if those changes, taken as a whole, could significantly affect safety or effectiveness. After assessing each change individually, manufacturers should assess all changes made since the last 510(k) clearance collectively to determine whether the collective sum of all changes triggers the requirement for a new 510(k) submission.

- Whenever manufacturers change their device, they must comply with the Quality System (QS) regulation (21 CFR Part 820) unless the device in question is exempt from the QS regulation. This regulation requires that specification changes be documented, validated or, where appropriate, verified prior to their implementation.

- Manufacturers should have a mechanism or standard operating procedures in place for evaluating whether a proposed change meets the regulatory threshold for a new 510(k). Once a manufacturer has fully considered the device modifications:

    - If there are multiple changes and analysis of any one of the changes results in a determination that submission of a new 510(k) is required, then the manufacturer should submit a 510(k) that incorporates all of the planned changes as well as a comparison of the changed device to the device as it was described in the most recently cleared 510(k). All changes to the device since its most recent 510(k) clearance should be identified, even those that did not trigger the need for a new 510(k); the specific change(s) that triggered the 510(k) should be distinguished. Note that a table is often helpful for such comparisons.

    - If a manufacturer determines that its device modification(s) could not significantly affect safety or effectiveness and therefore decides not to submit a new 510(k), it should document the basis for concluding that it does not require a 510(k). Manufacturers should scientifically justify their conclusions that modifications, individually and collectively, could not affect safety or effectiveness. A copy of this documentation should be maintained. It is recommended that manufacturers answer each question below to satisfy basic Quality System requirements for documenting device modifications. *See* 21 CFR 820.30 and 820.70(b).

This guidance does not address every type of change to every type of device, and there will still be decisions in a "gray area" that manufacturers will have to make. For those circumstances where the proposed change is not addressed in this guidance or in a device-

specific guidance document, manufacturers are encouraged to contact the appropriate review divisions to obtain advice.[7]

Important Note on 510(k) Devices that Contain Nanomaterials or Otherwise Involve the Application of Nanotechnology[8]:

Nanotechnology is a new and evolving field for both the medical device industry and the Agency. At this time, FDA has not adopted nanotechnology-specific criteria to assist manufacturers in determining when a change to a device that contains nanomaterials or otherwise involves the application of nanotechnology rises to the level of significance that requires submission of a new 510(k). For this reason, FDA recommends that manufacturers consult with the agency for any nanotechnology-related changes to devices to determine whether and how the change may affect the safety or effectiveness of the device. FDA plans on developing additional guidance to further explain the Agency's thinking on this matter. Contact the appropriate review division with any questions on devices that contain nanomaterials or otherwise involve the application of nanotechnology.

V. Manufacturing Process Changes

Under 21 CFR 807.81(a)(3), a new 510(k) is required for a significant change or modification in manufacturing process that could significantly affect the safety or effectiveness of the device. The questions below address whether manufacturing changes constitute significant changes that would require a new 510(k), and provide examples of when a 510(k) is or is not required.

1. Was manufacturing process information part of the original 510(k) submission?

Manufacturing process changes will be particularly important for devices where the manufacturing process information was reviewed in the original 510(k) submission. Certain devices, such as contact lenses and wound dressings, typically involve review of manufacturing process information.[9] Other devices may include manufacturing process information in the 510(k) in order to address specific concerns, and some devices may

---

[7] See *CDRH Management Directory* or *CBER Key Staff Directory*

[8] **Nanotechnology, Nanomaterial:** FDA has not adopted a formal definition of "nanotechnology," "nanomaterial," "nanoscale," or related terms. In the absence of a formal definition, FDA developed the following points to consider in determining whether a FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology: (1) whether engineered substances have at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or (2) whether engineered substances exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer. Once finalized, the agency intends to apply these considerations broadly to all FDA-regulated products, including medical devices. For additional information, see FDA's draft guidance to industry titled "*Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*."

[9] See device-specific guidances for contact lenses and wound dressing devices, e.g., *Premarket Notification Document (510(k)) for Daily Wear Contact Lenses* and *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Wound Dressing with Poly(diallyl dimethyl ammonium chloride) (pDADMAC) Additive*.

undergo a pre-clearance inspection (e.g., infusion pumps – see *Draft Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification (510(k)) Submissions*). In cases such as these, where manufacturing processes factor into the original clearance decision, the Agency has indicated that there is a higher likelihood that manufacturing process changes could significantly affect safety or effectiveness. Therefore, in cases where review of an original 510(k) submission includes a review of manufacturing process information, changes to manufacturing processes that could affect device specifications will likely require submission of a new 510(k). (Manufacturers should be aware of these requirements as they apply to their device type. Contact the appropriate review division with any questions.)

Device specifications include performance specifications (such as measurement accuracy), or physical or material characteristics (such as tensile strength). Changes to device specifications can significantly affect the performance of a device, and thus significantly affect a device's safety and effectiveness. Changes to these specifications may be unintended collateral changes. For example, a new manufacturing process might leave a residue on an implant and change the surface chemistry of the device, causing it to react differently to the in vivo environment, or a change in heat treatment of an alloy might significantly affect the alloy's physical properties, causing it to fail early.

2. Is there a change in packaging or expiration dating?

Generally, changes in device packaging or changes in the expiration date for use of a device do not result in the need to submit a new 510(k). Such changes are properly within the scope of the Quality System regulation. This conclusion is true whether the manufacturer applies an expiration date because of package integrity considerations, e.g., sterility, or because of a finite shelf-life of the device. However, where methods or protocols not described in the original 510(k) are used to support new package integrity or shelf-life claims, submission of a new 510(k) may be necessary. When such methods or protocols are described in the original 510(k), FDA reviewers should evaluate them with possible future use of the method or protocol in extended testing in mind.

3. Has there been a change in sterilization?

Changes in sterilization have the potential for changing the performance characteristics of a device. If these changes could significantly affect the safety or effectiveness of the device, the changes in sterilization methods trigger the requirements for a 510(k) submission. When manufacturers make changes in sterilization methods, they should document that the important properties and specifications of the device remain unaffected as part of their compliance with the QS regulations. In addition, if the sterility assurance level (SAL) is changed, manufacturers should consider whether device safety or effectiveness may have been compromised by the new level. If the SAL remains better than 10^{-6}, a new 510(k) submission is not necessary; only if the SAL is less than 10^{-6} should a 510(k) be submitted. Changes to the sterilization method, such as changing from moist heat sterilization to e-beam radiation, require a new 510(k). Changes that result in a device being provided non-sterile when it was previously provided sterile, or vice-versa, also warrant a new 510(k).

VI. Labeling Changes

Changes in device labeling often pose the most difficult questions to be addressed by device manufacturers when deciding whether a new 510(k) submission is necessary. Frequently, an apparently subtle change in a device's labeling can have a significant impact on the safe and effective use of the device.

In order to properly consider labeling changes, it is important to keep in mind that the term "labeling" includes more than just the instructions for use. According to the FD&C Act, labeling means all written, printed, or graphic matter on or accompanying a medical device.[10] Labeling can therefore include things such as instructions that are displayed on a screen by software, stickers or text placed on a control unit, and promotional materials.

We recommend that manufacturers consider the following questions to determine whether a labeling change requires submission of a new 510(k):

1. Does the change affect the indications for use?

For the purposes of this discussion, "indications for use" refers to a description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient for which the device is intended.[11] FDA views most labeling changes that affect the indications for use, as just described, whether made to a specific indications section of the labeling or not, as major changes to the intended use of a device that warrant the submission of a 510(k).

FDA would not consider a change in the indications for use that removes certain indications or limits use within the currently cleared indication *due strictly to marketing reasons* to be a major change in intended use under 21 CFR 807.81(a)(3) that requires submission of a new 510(k). For example, if a device was cleared for use with three indications and the firm decides to market the device for only two of those indications due to changes in market demand, FDA generally would not consider this to be a "major change" under the rule that would require submission of a new 510(k). However, if a firm decides to market the device for only two of those indications due to other reasons, for example, changes that have been made to the device that affect the removed indication or because of complaints or corrective actions, FDA would generally consider the removal of the indications for use to be a "major change" that requires a new 510(k).

Four other common labeling changes that affect the indications for use and that FDA believes would usually require submission of a 510(k) are:

- Changes that allow reuse of devices previously labeled "single use only"
- Changes from prescription to over-the-counter (OTC) use

---

[10] §201(m): "The term 'labeling' means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."

[11] The term indications for use is defined in the PMA regulation at 21 CFR 814.20(3)(i). We have applied the definition in the same way in the 510(k) context.

- Changes from prescription use in a clinical setting to prescription use in a home setting (home use devices[12])
- Changes from general patient populations to specific patient populations (e.g., changes from an undefined patient age group to a pediatric population)

2. Does the change affect the contraindications for use?[13]

a. Does the change add a contraindication?
While all changes in the labeled contraindications for device use should be reviewed by the Agency, FDA recognizes that, in general, the addition of a contraindication based on new information is important to public health and should be implemented immediately. To facilitate the timely implementation of such changes, manufacturers are encouraged to add new contraindications to labeling of cleared devices and to notify existing device users of such contraindications as expeditiously as possible whenever a pressing public health need arises. The new labeling should be submitted to FDA as part of a new 510(k) that is prominently labeled "change being effected" (CBE). Manufacturers may market the device with the modified labeling unless otherwise notified by FDA (FDA may ask for revisions during review of the 510(k)).[14] Manufacturers should be thoroughly familiar with what constitutes a true contraindication to make a change effective before clearance; if there are any questions, contact the Agency before proceeding.

b. Does the change delete a contraindication?
Manufacturers planning to delete a contraindication should submit a new 510(k) prior to effecting the change because this type of labeling change expands the indications for use. For example, if a physical restraint was contraindicated for use with individuals weighing less than 100 pounds and the manufacturer subsequently wishes to remove this contraindication, a 510(k) should be submitted and cleared prior to marketing the device with the new labeling.

3. Is it a change in instructions for use?

If the labeling change instructs the user to use the device in a different fashion from that originally cleared, then this could lead to new significant safety risks or less effective use of

---

[12] For purposes of this guidance, FDA considers a home use device to be a medical device intended for users in a non-clinical environment that is managed partly or wholly by the user. These devices require adequate labeling for the user and may require training for the user by a licensed health care provider. Please see http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/HomeUseDevices/default.htm.

[13] Contraindications describe populations in whom or situations in which a device should not be used because the risk of use clearly outweighs any reasonably foreseeable benefits. See the Blue Book Memorandum G91-1, *Device Labeling Guidance*.

[14] Note that FDA considers the addition of new contraindications to be a major change in intended use that requires submission of a 510(k). Before submission and clearance of a 510(k), the device with the changed intended use is adulterated under § 501(f)(1)(B) of the FD&C Act and misbranded under § 502(o) of the FD&C Act. However, FDA intends to exercise enforcement discretion with regard to these violations where manufacturers immediately implement a change in contraindications in order to protect the public health, as long as a new 510(k) labeled "change being effected" is submitted to FDA concurrently.

the device. FDA views changes of this nature as major changes in intended use that require submission of a 510(k). Such changes are likely to significantly affect safety or effectiveness and therefore should generally be reviewed by the Agency in a 510(k) prior to marketing. Note that changes in instructions may or may not also constitute changes in indications for use.

Examples:

- Labeling for a device that provides diagnostic information is modified to include additional or new instructions on how to interpret data from the device. FDA considers this change a major change in intended use that could significantly affect the treatment of the patient and that requires submission of a 510(k).

- Labeling for a cutting instrument or laser is modified to include additional or new instructions about incision procedures. FDA considers this change a major change in intended use that could significantly affect the safety and effectiveness of the device's treatment of the patient and that requires submission of a 510(k) prior to marketing.

4. Is it a change in warnings[15] or precautions?[16]

Manufacturers should monitor device usage to facilitate continuous upgrades of device labeling and promptly revise the warnings and precautions sections based on use experience. Events that precipitate changes of this type should be reported under the Medical Device Reporting regulation (MDR), 21 CFR Part 803. Submission of a new 510(k) for labeling changes that add warnings or precautions is generally unnecessary; however, manufacturers are encouraged to discuss these situations with FDA. Labeling changes that delete warnings or precautions, however, could be changes in intended use that affect how a device is used and could therefore have a significant effect on safety or effectiveness. These changes are likely to warrant new 510(k) submissions.

5. Is it some other labeling change?

Other types of labeling changes might include clarifications to language that do not change the meaning, aesthetic or organizational changes to the way information is displayed, or logo or name changes. These types of changes are not usually considered major changes to the intended use and will not typically require a new 510(k). For example, the instructions for use of an automated clinical chemistry analyzer may be modified to clarify how routine batch testing operation may be temporarily interrupted to allow efficient processing of high priority samples.

---

[15] Warnings describe serious adverse reactions and potential safety hazards along with consequent limitations in use and mitigating steps to take if they occur. See the Blue Book Memorandum G91-1, *Device Labeling Guidance*.

[16] Precautions describe any special care to be exercised by a practitioner or patient for the safe and effective use of a device. See the Blue Book Memorandum G91-1, *Device Labeling Guidance*.

VII. Technology, Engineering, and Performance Changes

To determine whether a technology, engineering, or performance change requires a new 510(k), manufacturers should first review the labeling questions above, as technology changes sometimes affect device labeling, then review the following questions. Even if labeling has not been affected, a new 510(k) submission should generally be submitted for modifications to device technology, engineering, and performance that significantly affect the cleared Indications for Use or fundamental technology of the existing device, or that substantially change the performance characteristics or specifications of the device. These types of modifications encompass a broad span of changes, from minor engineering changes in a circuit board layout to a change from electromechanical to microprocessor control of device function.

Although the examples provided under each question below generally refer to specific device types, these examples are intended to be pertinent to similar types of changes involving different devices.

1. Does the change alter the fundamental scientific technology of the device?

The fundamental scientific technology of a medical device encompasses both the design principle – the underlying scientific principle by which the device performs its intended therapeutic or diagnostic function – and the method by which that principle is applied. While many changes to the technology and design of a medical device discussed in this section of the guidance do not trigger the requirement for a new 510(k), all changes in fundamental scientific technology could significantly affect safety or effectiveness. Therefore, such changes require the submission of a new 510(k).

Examples:

- A humidifier is designed to add moisture to the air. The design principle of such devices is that water droplets must be separated and dispersed in order to add moisture to the air. Two applications of this principle that achieve the intended use are (1) vibrating piezoelectric material under a quantity of water (separation and dispersion of water molecules by high frequency vibration), and (2) using a wick to spread water, and a fan to disperse water droplets over a wide surface area such that an adequate threshold of airflow can disperse the molecules. These two mechanisms use the same design principle, but apply it in different ways. A device modification from one application mechanism to the other could significantly affect safety and effectiveness, and should therefore result in a new 510(k) submission.

- A device is changed from analog to digital control. This change is considered a change in the fundamental scientific technology of a device. While the change to digital control can markedly improve device performance specifications and effectiveness, the integration of a digital control into a previously all-analog system is complex and usually undertaken only as part of a major redesign of a product that could significantly affect safety or effectiveness. Thus, a new 510(k) should be submitted prior to marketing.

- A manufacturer of a computed tomography x-ray system who changes the image reconstruction algorithm from simple back projection to a new, modified method is changing the fundamental scientific technology of its device. This type of change could significantly affect safety and effectiveness and should therefore be reviewed in a new 510(k).

- A manufacturer wants to modify the component of a hemodialysis delivery system that is responsible for maintaining the fluid balance of the dialysis treatment (i.e., the amount of fluid that is removed and returned to the patient). Because this change could directly impact the safety or effectiveness of the fluid balancing algorithm, and therefore the safety or effectiveness of the treatment, a new 510(k) should be reviewed prior to marketing.

2. Is it a change in energy type?

Energy type refers to the type of power input to or output from the device. Changes in energy type are a change in design that will always have a significant effect on safety or effectiveness because power inputs and outputs are typically critical to proper device function. Most of these changes should be reviewed in a new 510(k) prior to marketing.

Examples:

- A device that is changed from an external power source to battery power should result in submission of a new 510(k).

- A device that is modified to use radiofrequency (RF) energy instead of microwave energy, for instance, in an ablation device changes how the device functions and could significantly affect safety and effectiveness. (This change could also be considered a change in fundamental scientific technology.) This change should result in a new 510(k) submission.

3. Does the change have the potential to significantly alter the performance characteristics or specifications of the device?

Such changes directly impact the performance, and potentially the safety and effectiveness, of the device and a new 510(k) with comparative testing should be provided for such modifications, whether the performance characteristics are improved or worsened.

Examples:

- A currently marketed pulse oximeter is only sensitive to an oxygen saturation of 90%, and a manufacturer wants to modify the device to be sensitive down to a concentration of 70%. While this change is an improvement in the device's capabilities, the performance specifications of the device are being altered, which could significantly affect safety or effectiveness. A new 510(k) submission should be provided.

- A manufacturer modifies a hemodialysis catheter to make the device more flexible and kink-resistant. Even though these changes are intended to increase the safety and effectiveness of the device, the modifications potentially alter the performance characteristics and safety and effectiveness of the device and therefore a new 510(k) should be submitted.

- A manufacturer wants to modify its immunoassay from monoclonal to polyclonal (or vice versa) or to recombinant monoclonal to improve performance. This change could significantly affect safety or effectiveness so a new 510(k) should be submitted.

4. Is it a change in ergonomics or the patient/user interface?

Changes of this type may significantly affect the safety or effectiveness of the device, but not all such changes do. The factors to consider in determining whether such a change requires submission of a new 510(k) are whether the change can expand how the device will be used or affect how it will perform. Changes that are made only to increase comfort and could not result in a corresponding improvement (or decline) in safety and effectiveness are unlikely to warrant a new 510(k); however, one must consider how each of these changes might affect safety or effectiveness. Simple design changes may have unintended consequences, as illustrated by the first example below.

Examples:

- A surgical handpiece handle is modified to make the device less bulky and easier to wield by relocating the motor closer to the proximal end of the device. While this change may be intended to increase user comfort, the motor could be too close to the treatment area on the patient or to the user's hand and cause burns, or the mechanical performance of the device could be affected. Since this change could significantly affect the safety or effectiveness of the device, a new 510(k) should be submitted.

- The device handle of an endoscopic suturing device is modified to change the molded shape to a more ergonomic design, rounding square corners for physician comfort. Only the handle is modified and the functional portions of the device remain unchanged. This ergonomics change is unlikely to significantly affect safety or effectiveness. FDA would not expect a new 510(k) in this instance.

- A mask used for CPAP (continuous positive airway pressure) is modified to use a new, softer material for increased patient comfort. Since this change could affect the fit of the mask on the patient's mouth and the pressure used to keep the airway open for unobstructed breathing, safety and effectiveness could be significantly affected, and a new 510(k) should be submitted.

- A manufacturer wants to change a coded calibrator glucose meter to a "no code" glucose meter, i.e. a factory calibrated meter, eliminating the need for the patient to calibrate the device. This patient/user interface change could significantly affect the safety or effectiveness of the device, and a new 510(k) should be submitted in this instance.

- The interface of a dental surgical unit is modified to improve the display of treatment parameters in an effort to improve communication of information during treatment. While such a change could affect the safety and effectiveness of the device, the Agency would not generally consider this change significant, and therefore would not expect a new 510(k).

5. Is it a change in dimensional specifications?

Dimensional changes can, but do not always, significantly affect safety and effectiveness. Whether or not they will depends on the device type and the component being modified. For example, the dimensions of the casing of a typical ventilator unit do not significantly affect the safety or effectiveness of the device, however, the length of the ventilator hose is directly related to the effectiveness of the device as a longer hose will require higher pressure to circulate air. FDA recommends that manufacturers consult the appropriate review division regarding any questionable dimensional change. Typically, dimensional changes that change a device dimension that is related to the performance of the device outside of the cleared dimensional tolerance range have the potential to significantly affect safety or effectiveness. For instance, if a device is cleared with a length of 10.0 mm ± 0.5 mm, a modification that makes the length 10.5 mm would not be significant (please note that a second change that makes the length 11.0 mm would be outside the tolerance range of the originally cleared device and thus be significant). Device dimensions that are modified beyond tolerance ranges will usually warrant a new 510(k), although modifications within previously cleared size ranges typically will not (see second example).

Examples:

- A biliary stent is modified to have a longer length (outside of its dimensional tolerance range). The length (or diameter) of a biliary stent is an essential characteristic of the device, and even a small change can significantly affect the safety or effectiveness of the device, even if it is in between currently marketed sizes. Therefore, a new 510(k) should be submitted for this change.

- A manufacturer of a bone plate whose last 510(k) included 2 and 4 mm thick variations introduces a 3 mm thick version of an otherwise identical plate. This modification would not require a new 510(k), as no new risks are being introduced. (However, a new version of the bone plate that is outside the cleared 2-4 mm thickness range may introduce new risks and should therefore result in a new 510(k) submission.)

- The case of an infusion pump is increased in size in order to facilitate a larger display panel. The size of the internal pump mechanism is not modified. This change is not likely to significantly affect the safety or effectiveness of the device because the modified dimension is not directly related to the performance of the device, and therefore the manufacturer does not need to submit a new 510(k).

6. Is it a change in software or firmware?

Small changes to device software – including software that is an integral part of a device or stand-alone software that constitutes a medical device in and of itself – can have pervasive effects on the safety or effectiveness of a device and trigger the need for a new 510(k) submission. However, some low risk changes may be made by following the QS regulation (including design controls) and documenting the appropriate validation testing. The factors to consider in determining whether such a change requires a new 510(k) are whether the software change could expand the capability of the device or affect device performance. Such changes will likely warrant a new 510(k). Changes to device software that could affect a clinical algorithm (an algorithm that controls how software analyzes, interprets, or uses patient data) would also warrant a new 510(k).

Examples:

- Software that plans placement of an implant based on patient case data is modified to plan placement of different implants or to plan placement based on a new patient parameter. These changes should result in a new 510(k).

- Software for a dental operative unit is modified to allow for use of a new control feature. This change should result in a new 510(k).

- Software for an electroencephalograph (EEG) is configured to display a generic error message when a sensor is disconnected. The software is modified to display a more specific error message that instructs the user to connect the disconnected sensor. This change does not significantly affect the safety or effectiveness of the EEG and does not require a new 510(k).

- The software for a polysomnogram (PSG) is modified to allow for saving or printing of recorded information for post-acquisition viewing. This change does not significantly affect the safety or effectiveness of the PSG and does not require a new 510(k).

7. Does the modification impact how the device receives, transmits, or displays electrical signals or data?[17]

While such changes may seem innocuous, most changes of this nature have the potential to significantly impact safety or effectiveness by altering data communication quality and therefore should result in a new 510(k) submission. Also see *Deciding When to Submit a 510(k) for a Change to an Existing Wireless Telemetry Medical Device*.

Examples:

[17] Note that Medical Device Data Systems (MDDS) are exempt from 510(k) requirements, see 21 CFR 880.6310, and are outside the scope of this draft guidance. For more information on MDDS, see http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/MedicalDeviceDataSystems/default.htm.

- Diagnostic software that typically displays images on a monitor in a clinical setting is modified to output the image to a portable hand-held device that can be used to view the images from any location. This change could result in new risks, such as the inability to discern certain data due to a smaller hand-held screen, lower picture resolution, or loss of data during transmission, that could significantly affect the safety and effectiveness of the software. Therefore, this change should result in a new 510(k) submission.

- An infusion pump that was cleared with a hard-wired connection to a keyboard to input treatment parameters is modified to include wireless capability to allow for remote input of treatment parameters. This change could significantly affect safety or effectiveness by altering data communication quality, which could affect the input of treatment parameters, and should therefore result in a new 510(k).

8. Is the modification intended to add an aspect of autonomous or semi-autonomous control to the existing device?

Any device modification that takes control of the device away from the user or is used to assist or take away decision-making from a user likely introduces new risks that could significantly affect safety or effectiveness, and should be reviewed in a new 510(k) submission prior to marketing.

Examples:

- A colon imaging software package is modified to include computer assisted detection to assist the physician in determining potentially malignant tissue. As a new feature, this change could significantly affect the safety or effectiveness of the device by introducing the possibility of false positives or negatives that could adversely affect the course of treatment. This change requires a new 510(k).

- A dental handpiece is modified to automatically increase or decrease the revolutions per minute (rpm) of a drill bit based on treatment selected or the type of bone encountered. Automating this treatment parameter introduces several new risks, such as an inappropriate automatic increase to an unsafe rpm or an inappropriate automatic decrease to an ineffective rpm. These risks constitute significant effects on safety and effectiveness. This change requires a new 510(k) prior to marketing.

- A device that acquires nerve conduction waveforms and extracts multiple parameters from those waveforms is modified to include software that automatically compares the parameters to a reference database to provide a diagnosis. An automated diagnosis can influence patient treatment and could significantly affect the safety and effectiveness of the device. This change requires a new 510(k).

9. Is the change being implemented to address a specific risk or failure mode for your device?

Changes that are implemented to address either known or newly identified safety risks or failure modes of a device, including those intended to address a known device- or user-

related adverse event or complaint, are by definition likely to significantly affect safety or effectiveness, even if the modification is intended to make the device more safe than the previous version. These modifications may include the implementation of new alarms or new alarm setpoints, modifications to the user interface to display new information that may be used to manage device settings, or design modifications that are intended to eliminate known failure modes. These changes should usually result in new 510(k) submissions.

These situations may also call for a device recall. You should contact the CDRH Office of Compliance or the Office of Compliance and Biologics Quality in these cases, and if a recall is initiated, consult the Blue Book Memorandum K95-1, *510(k) Requirements During Firm-Initiated Recalls*.

Examples:

- A manufacturer of a fluid warming device wants to add a protective mechanism (either hardware or software) to cut off power to the device should the fluid temperature increase past a certain setpoint. This change also addresses a specific risk, and could significantly affect safety or effectiveness. This change should result in the submission of a new 510(k).

- A manufacturer wants to add a color-coded luer or proprietary connector to address the risk of misconnections for a feeding tube. A change of this type should result in the submission of a new 510(k).

10. Does the change affect how the device is likely to be used in practice?

Technological or design changes may affect how a device is used in practice, and therefore affect the safety or effectiveness of the device, even if no change in the Indications for Use statement accompanies the change. Such changes may create the need for new directions for use or a limitation in the device labeling to address the potential that an off label use could cause harm.[18] Particularly when the modification could create a reasonable likelihood of off-

---

[18]The FD&C Act provides in section 513(i)(1)(E)(i) that:

Any determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k). However, when determining that a device can be found substantially equivalent to a legally marketed device, the director of the organizational unit responsible for regulating devices (in this subparagraph referred to as the "Director") may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing—

(I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and

(II) that such use could cause harm.

FDA would make such a finding in writing where it determines that such a change is reasonably likely to result in an off-label use that could cause harm.

label use that could cause harm, a new 510(k) should be submitted to allow FDA to determine whether a change to the labeling is necessary, even if the manufacturer does not intend a change to the indications for use in the labeling. The questions below are intended to guide manufacturers in determining whether changes to device technology, engineering, or performance constitute significant changes that trigger the need for a new 510(k) to enable FDA to evaluate whether "appropriate information" in the labeling about a use not currently identified in the labeling is necessary.

a. **Is the modification to the device likely to alter or expand the use of the device?**
If an existing device is being modified to allow for its use in a different or modified type of medical procedure, or to treat or diagnose a disease or medical condition apart from what has been previously cleared, the potential to significantly affect safety or effectiveness will be high, and therefore, these changes should result in a new 510(k) submission.

Examples:

- A manual surgical instrument is modified so that it can be connected to an electrical stimulator and conduct current (i.e., is now both a surgical instrument and an electrode). This change should be submitted in a 510(k) prior to marketing.

- The length of a surgical scissor is modified such that an existing device previously intended for only open surgical procedures can now be used for closed, endoscopically-controlled procedures. This change should be submitted in a 510(k) prior to marketing. (Note that while a typical surgical scissor is exempt from submitting a 510(k) by regulation, 21 CFR 878.4800, a 510(k) submission may be necessary in this instance because the change may alter the intended use of the device or may involve a different fundamental scientific technology than the generic type of device (21 CFR 878.9(a), (b)).)

- An in vitro diagnostic test is modified such that the processing utilizes frozen biopsy tissue samples rather than paraffin embedded tissue samples, so that users have more flexibility in tissue processing. This change could significantly affect the device performance and therefore should be submitted in a 510(k) prior to marketing.

b. **Does the modification allow for the use of the device in a new, expanded, or more specific patient population?**
Design changes that allow use in a new, expanded, or more specific patient population also carry a high potential to significantly affect safety or effectiveness, and therefore, these changes should result in a new 510(k) submission.

Examples:

- New features of a ventilator allow the device to be used for the treatment of pediatric patients, whereas previously it was only cleared for use by patients who had a tidal volume in the adult range. This is an example of an expanded patient population that should result in a new 510(k).

- The dimensional specifications of a feeding tube are reduced to facilitate use of the device in an infant by making the implanted portion shorter and the tubing diameter smaller and thus more appropriate for the slower flow rate and volume necessary for use of the device in an infant. This is an example of a more specific patient population which should result in a new 510(k).

- An evoked response auditory stimulator intended to aid in the detection of lesions in the auditory pathway for the general population is modified in order to detect lesions in a specific patient population, e.g., persons identified as having a higher level cognitive dysfunction thought to be related to hearing. This is an example of a device being modified for a more specific patient population. This modified device should be reviewed in a 510(k) prior to marketing.

c. Does the modification significantly change or alter an established medical procedure associated with the device?

Changes that result in an alteration to an established medical procedure should be reviewed in a new 510(k) prior to marketing because the new use of a device may introduce new safety risks or lead to less effective use of the device.

Example:

- Components of a surgical kit are combined with a surgical handpiece to allow cricothyroidotomy to be performed with one device. This device modification and its corresponding modified procedure could significantly affect the safety or effectiveness of the device and therefore should result in a new 510(k).

d. Is a specific modification intended to allow for the use of the device in a new environment in which there may be new risks affecting safety and effectiveness?

In general, modifications to allow a device to be used in a new environment are associated with new risks. Therefore, in most cases, changing a device to fit a new environment should result in a new 510(k) submission.

Examples:

- A stationary electrocardiogram (ECG) device originally cleared and intended for use in hospitals is modified to reduce lead sets or incorporate modular electrodes, which may allow use in pre-hospital settings such as ambulance transport. This change should result in a new 510(k) submission prior to marketing.

- If an electroencephalograph (EEG) seizure detection device originally intended for use in post hoc review of EEG data from epilepsy monitoring units is modified to add a real-time alarm, it may allow use in an intensive care setting.

Similarly, if an EEG device originally intended for general use is modified to reduce the number of electrodes, it may allow use in emergency settings. These changes would introduce new risks and therefore should be reviewed under 510(k) prior to marketing.

e. **Is the change intended to allow the device to be used by a lay person outside of a clinical setting?**
These changes may include those that change the indication of the device from prescription to over-the-counter, as well as those that allow the device to be used by a lay person outside of a clinical setting as prescribed by a physician (home use). Both types of changes introduce new risks that could significantly affect safety or effectiveness, and therefore should result in the submission of a new 510(k).

Examples:

- An ECG device is modified to reduce the number of leads or simplify electrode placement to allow for home use or over-the-counter use. This change should result in a new 510(k) submission prior to marketing.

- A hemodialysis machine is modified to incorporate additional safety features, a more friendly user interface, and a special user's manual so that it may be operated by a lay person. The potential for use by a lay person outside the clinical setting introduces new risks. This change should be reviewed in a new 510(k) submission prior to marketing.

f. **Does the modification allow for the device to provide new information or data to the user that could be used for patient assessment or diagnostic purposes?**[19]
New technological characteristics that allow use for patient assessment or diagnostic purposes could significantly affect the safety or effectiveness of a device and may necessitate a new 510(k). This principle applies even if the new patient assessment information is used as an aid or adjunct to other measures or is only considered additional information.

Examples:

- A device that previously only qualitatively displayed blood flow or stenosis by displaying an image is modified to output quantitative or semi-quantitative data for these assessments. This change from qualitative, or informational, data to quantitative data would introduce new risks for the device and significantly impact safety and effectiveness. A new 510(k) should be provided.

[19] For the purposes of this guidance, any device that provides data or information used to assess a patient's condition or treatment can be considered diagnostic. A device need not be indicated solely for screening or providing diagnoses to be considered diagnostic.

- A device that previously only derived four parameters from an EEG waveform is modified to derive two additional parameters from the waveform. This change should result in a new 510(k).

- A device that previously calculated four parameters from a waveform is modified to calculate a standard deviation or variance of those parameters to aid in detecting abnormalities of the waveform as a diagnostic tool. This change should be reviewed in a 510(k) prior to marketing.

- A device cleared only to acquire and display raw physiological data is modified to include software that automatically analyzes, interprets, highlights or extracts parameters from the physiological data. This change should result in a new 510(k) prior to marketing

VIII. Materials Changes

Firms making changes to the materials from which their device is manufactured should first consider the other types of changes discussed above and their impact on the decision regarding the need for submission of a new 510(k). For example, a change of material type might also engender a change in the labeling of the device (e.g., the removal of a contraindication or addition of a warning) or a change in performance specifications (e.g., a reduction in tensile strength). These collateral changes should be considered first.

The first consideration for devices undergoing a modification to the device material is whether the material contacts the patient. Patient-contact includes both direct and indirect contact, whether of very transitory or permanent duration. In general, material modifications to device components that cannot have direct or indirect contact with the patient do not significantly affect safety or effectiveness of the device and so do not require a new 510(k) submission, unless they affect the fundamental device technology or performance (e.g., preservatives, antibacterials, moving parts, structurally significant components, lubricants, etc.).

Direct contact is when a material touches any tissue or bodily substance of a patient while it is still in or on a patient. Indirect contact is when a material has the *potential* to come into contact with any patient tissue or bodily substance by some intervening material (such as a liquid or gas) by first coming in contact with the intervening material, which subsequently comes in contact with the patient tissue or bodily substance. For example, a catheter hub (the part of the catheter which is external to the patient) contacts the patient indirectly. Fluids and drugs are infused through the hub and directly into the patient and, therefore, materials in the hub should demonstrate biocompatibility.

While most implants contact patients directly, there are some exceptions that have materials that are not considered patient-contacting. An example is a spinal cord stimulator. The internal contents of these devices are not patient-contacting; they are hermetically sealed so that there is no material transfer, fluid transfer, or leeching out of any material internal to the device. The internal components do not need to demonstrate biocompatibility.

1. Is it a change in material formulation?

Material formulation includes the chemical composition of the material, including the ratio of constituents and ingredients and their interactions, and their related physical chemistry.

It is important to keep in mind that material formulation can be affected by the processing aids, catalysts, and residual contaminants that are not intended to be a part of the material but may be introduced by manufacturing, sterilization, or handling. Changes to these processes may indirectly result in changes to material formulation.

a. **Does the change affect patient-contacting materials (either direct or indirect)?**
   Changes in material formulation of patient-contacting devices or device components may affect the biocompatibility of the device. These changes may also affect material properties and the safe and effective performance of a device. Therefore, a new 510(k) should be submitted for changes in material formulation for patient-contacting devices or device components.

   While it is conceivable that material formulation changes that do not affect patient-contacting materials could impact the safety or effectiveness of a device, this outcome is not typical. For most material formulation changes of non-patient-contacting materials, it is appropriate to simply document the change.

2. Does the change involve the device surface?

Changes to a device coating or surface modification technique, including chemical formulation, method of application, or surface preparation (e.g., acid-etching, blasting, etc.) generally significantly affect safety or effectiveness and would require a new 510(k). Keep in mind that residual contaminants from manufacturing, sterilization, and other processes can indirectly change the device surface.

IX. Is clinical data necessary to determine substantial equivalence?

A manufacturer's determination that clinical data is needed because bench testing or simulations are not sufficient to assess the safety or effectiveness of a modified device is a sure sign that the modification could significantly affect safety or effectiveness and that a new 510(k) should be submitted. Note that this criterion does not necessarily apply to in vitro diagnostic devices, which have different testing requirements. Contact the appropriate review division within the Office of In Vitro Diagnostics if you have questions.

For the purposes of this guidance, clinical data is not only data acquired from prospective, controlled clinical trials but includes any data derived from human subjects.