

**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On April 8, 1994, FDA circulated for comment the first draft guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device."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The type of modifications addressed in the draft guidance include labeling changes, technology or performance specifications changes, and materials changes.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 writing to Heather S. Rosecrans, HFZ-404. For questions regarding the use or interpretation of this guidance, also contact Heather Rosecrans at (301) 594-1190.]

**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

<u>SECTION</u>	<u>PAGE</u>
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 <i>In Vitro</i> 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 regulation³, 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 policy⁷ 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 add a contraindication?** 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 statute¹⁷ 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 regulations²² 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:

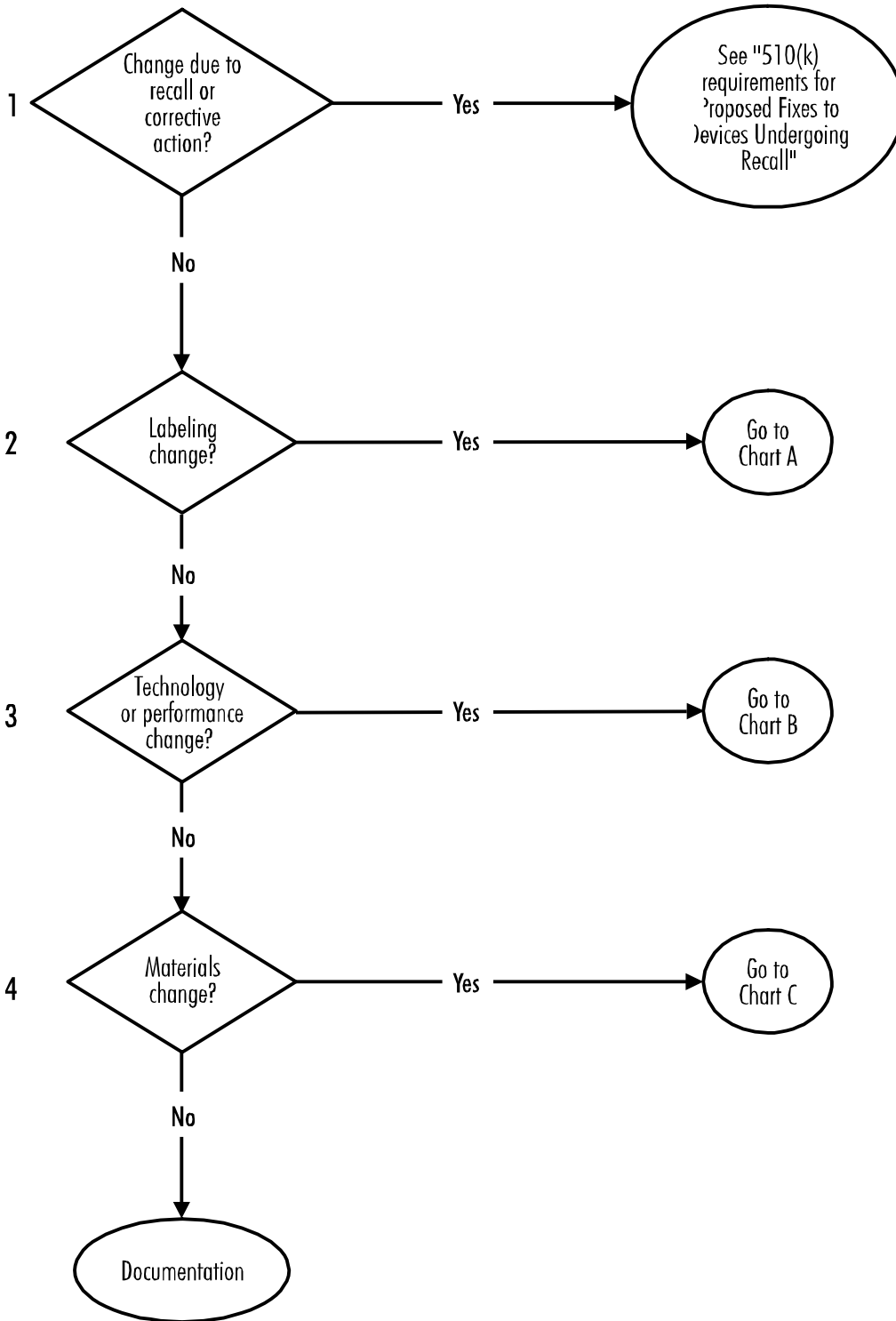
- Precautions describe any special care to be exercised by a practitioner or patient for the safe and effective use of a device. This definition also include limitations stated for IVDs.
- Warnings describe serious adverse reactions and potential safety hazards that can occur in the proper use or misuse 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.

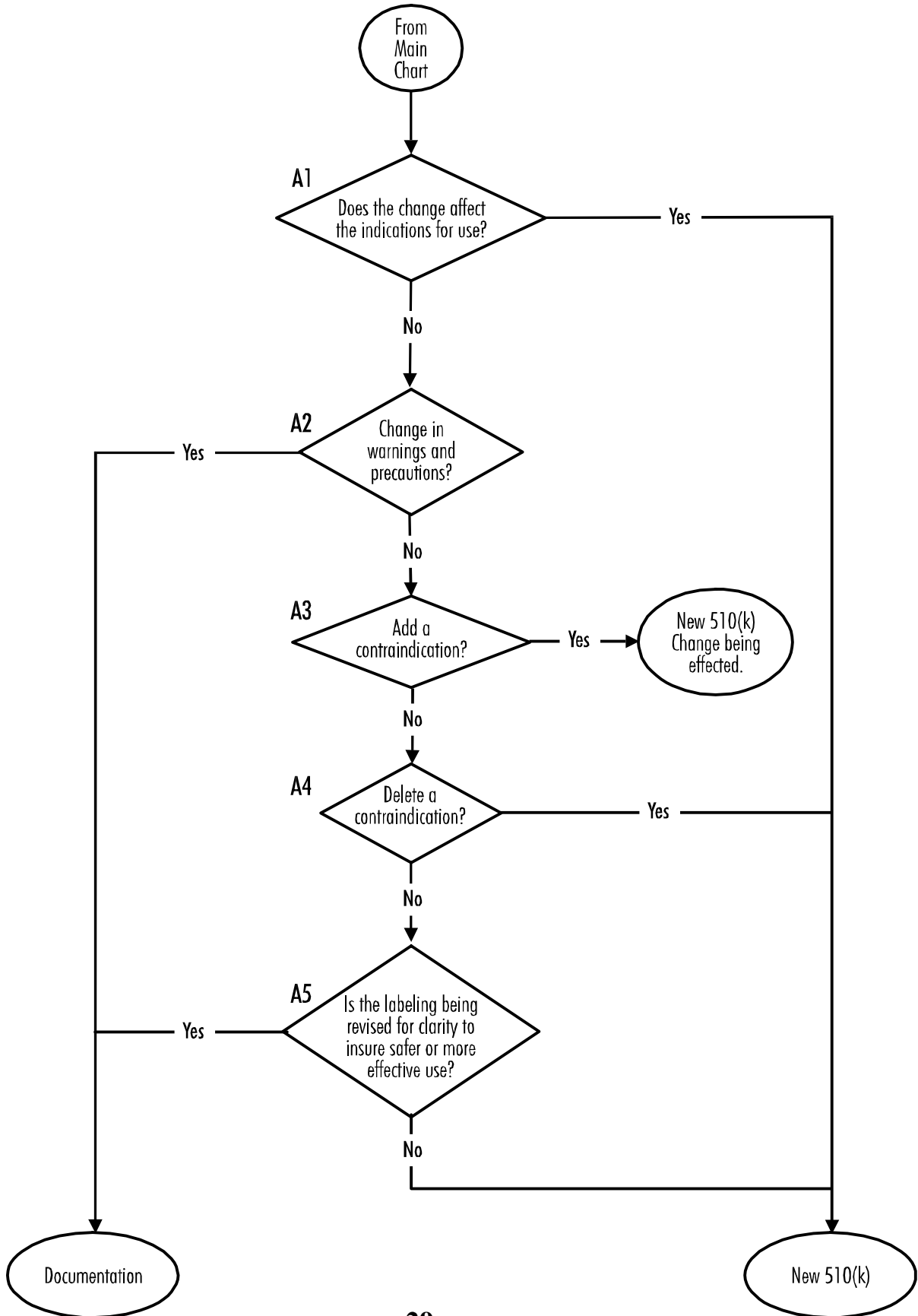
Software: The set of instructions used to control the actions or output of a medical device, to provide input to or output from a medical device, or to provide the actions of a medical device. This definition includes software that is imbedded or permanently a part of a medical device, software that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

Warnings: See “precautions, warnings, and contraindications” above.

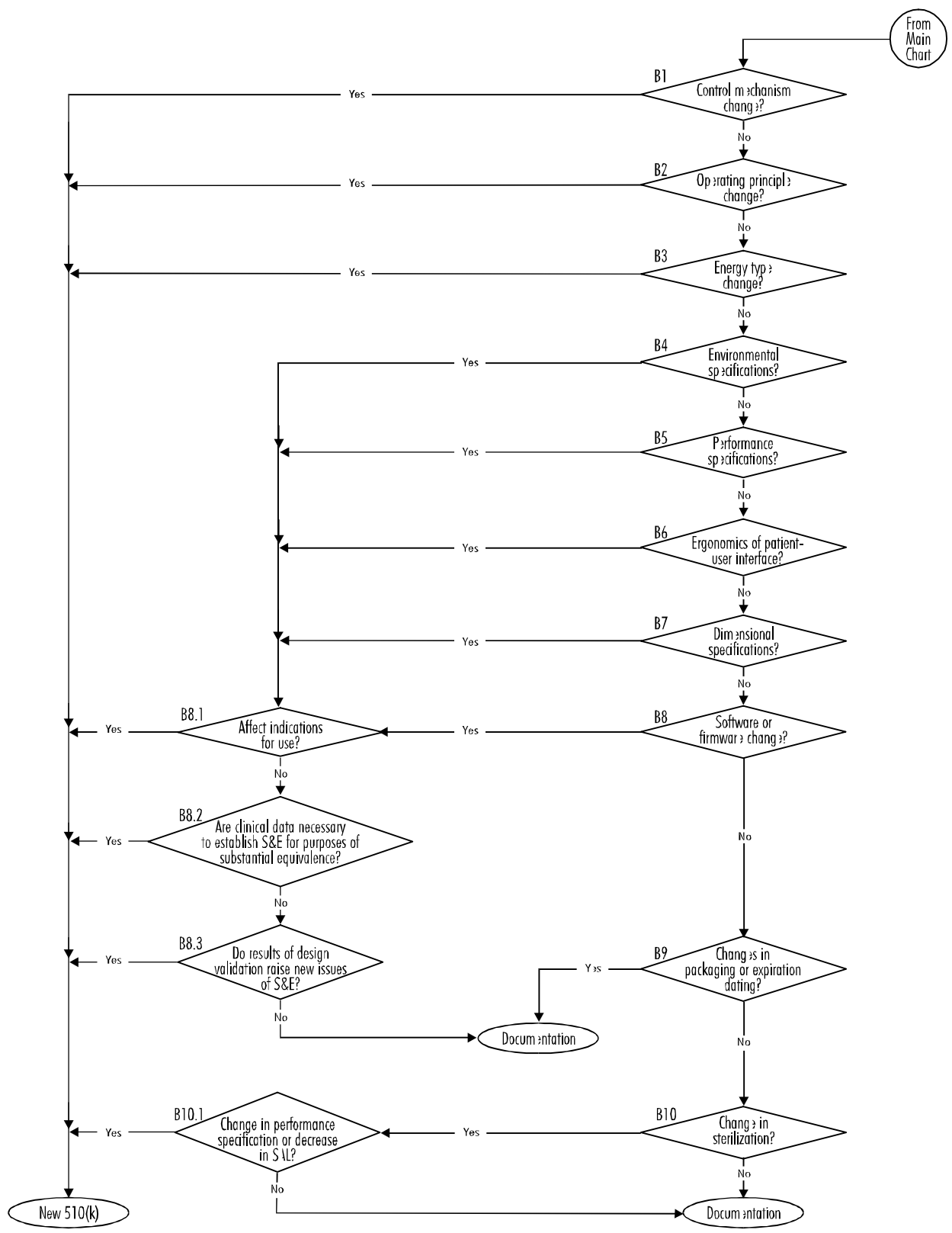
MAIN FLOWCHART WHEN TO FILE A 510(k) AFTER CHANGE TO A LEGALLY MARKETED DEVICE



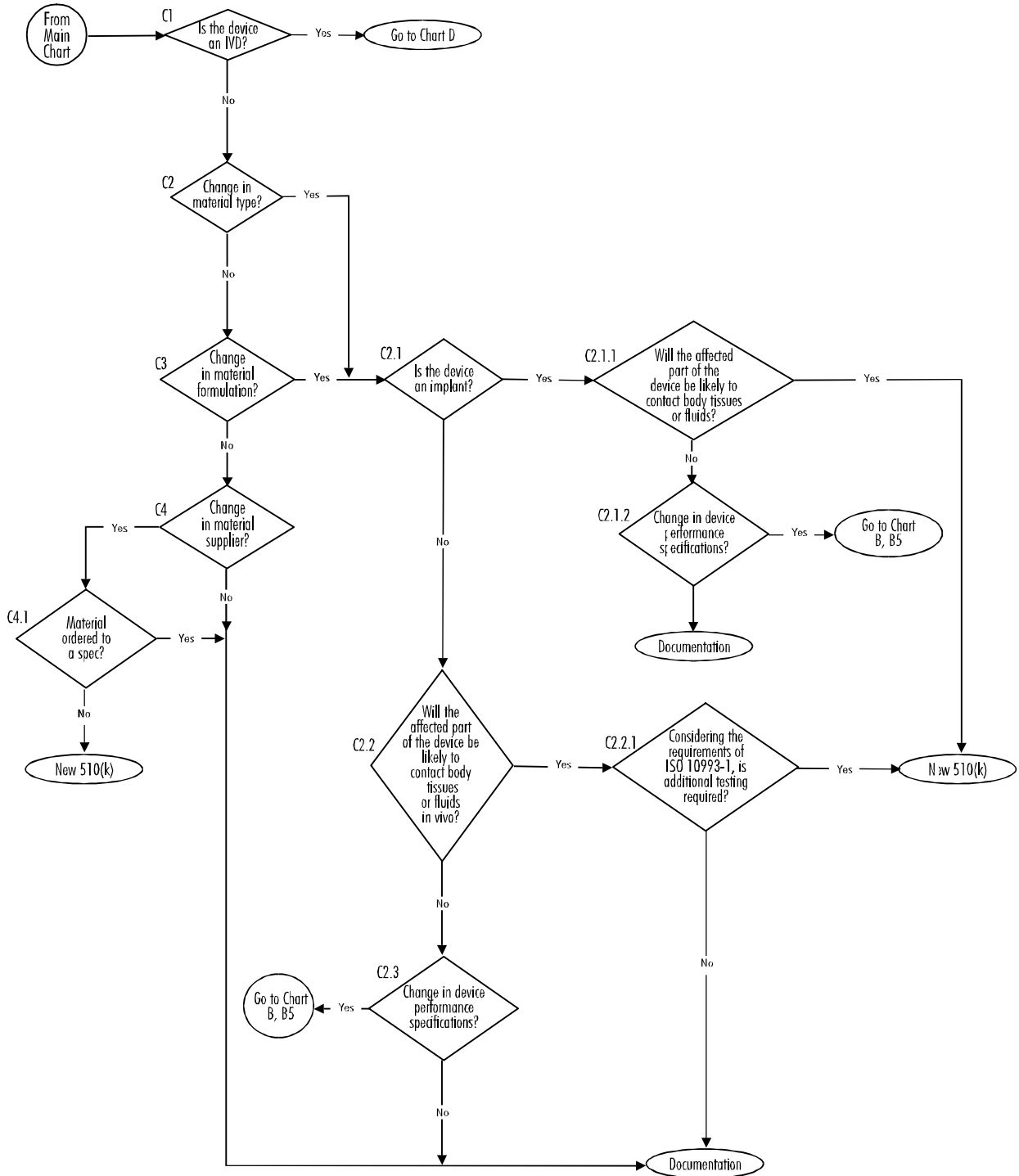
FLOWCHART A - IS IT A LABELING CHANGE?



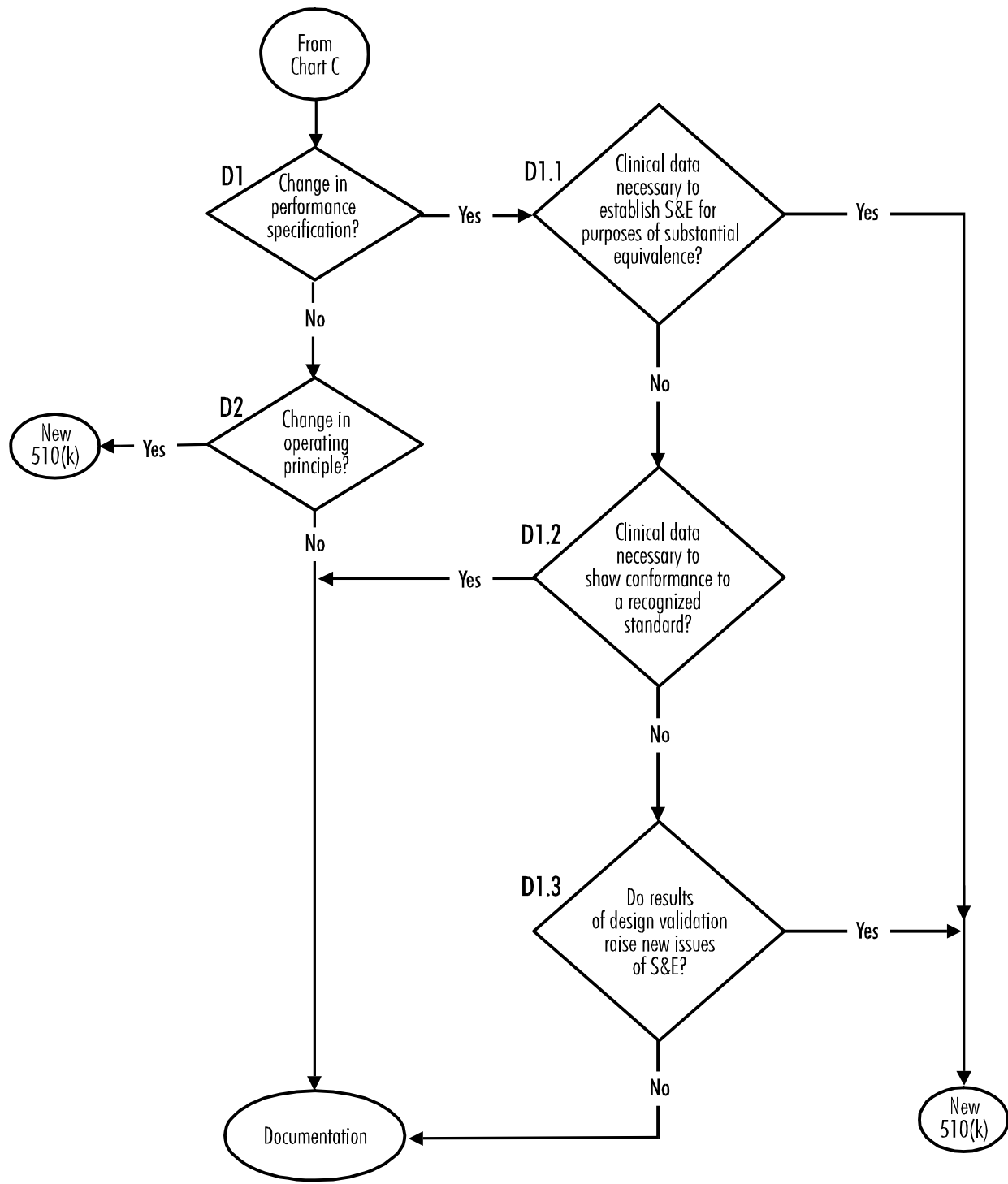
FLOWCHART B - IS IT A TECHNOLOGY OR PERFORMANCE CHANGE?



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 alloy	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 nitrogen strengthened ferritic martensitic austenitic	CoCrMo period CoCrWNi CoNiCrMo CoNiCrMoWFe CoCrNiMoFe Nickel based	CpTi (grade 1-4) Ti 6Al 4V Ti 6Al 7Nb Ti 5Al 2.5 Fe Ti 3.8Al15Mo5Zr Ti 13Nb13Zr Ti 12Mo6Zr2Fe Ti 15Mo2.8Nb.2Si NiTi alloy
Zr Alloys	Ta Alloys	Precious/Noble
Zr2.5Nb	unalloyed Ta	gold silver platinum palladium iridium Pt/Ir
Amalgams	Miscellaneous	
Ag-Hg Cu-Sn	aluminum copper mercury	

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)		
polyvinylidene 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
			HA/TCP
			hydroxylapatite
Carbon	Glass		
fibers	bioactive glass		
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.