Guidance for Industry

Modifications To Devices Subject to Premarket Approval - The PMA Supplement Decision Making Process

Draft Guidance – Not for Implementation

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

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Preface

Public Comment:

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 12420 Parklawn Drive (HFA-305), Room 1-23, Rockville, MD 20857.

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INTRODUCTION

In January 1997, FDA released a guidance document entitled “Deciding When to Submit a 510(k) for a Change to an Existing Device.” This document was an effort to elucidate and clarify current practice and FDA expectations regarding the process used to determine whether a change to a class I or II device or to a class III device for which premarket approval had not yet been required under section 515(b) of the Federal Food, Drug, and Cosmetic Act, (the act) (21 U.S.C. 360e(b)), required submission of a new 510(k). Application and use of this guidance provided a valuable tool for manufacturers to use to assist in the decision-making process for modifications to 510(k) devices.

Class III devices subject to premarket approval requirements under section 515 of the act were not addressed by that document, and the PMA regulation, 21 CFR Part 814, provides only general criteria for determining whether a PMA supplement is required for a particular device change. FDA’s process of developing specific guidance on submission of PMA supplements coincided with FDA reengineering activities, including the CDRH effort to streamline the PMA supplement process within the context of the existing premarket approval regulation. (21 CFR 814).

REGULATORY REQUIREMENTS FOR PMA SUPPLEMENTS

The current regulations for PMA supplements, at 21 CFR 814.39, identify a number of mechanisms for informing FDA of changes to devices that already have an approved PMA. One of these mechanisms, commonly referred to as the “PMA supplement,” involves in-depth review and approval by FDA prior to implementation of the change. The other mechanisms, including "Special PMA Supplement- Changes Being Effected", “annual (or periodic) reports,” and “document for file” which apply in specified situations, call for very limited or no FDA involvement prior to implementation. Clearly any effort to streamline the PMA process must take advantage, to the greatest extent possible, of these mechanisms.

The standard for determining whether a supplement must be reviewed and approved by FDA prior to implementation of a change to a device that is the subject of an approved PMA is contained in the regulations in 21 CFR 814.39. That section states:

> (a) After FDA approval of a PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA, unless the change is of a type for which FDA, under paragraph (e) of this section, has advised that an alternate submission is permitted. While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant shall submit a PMA supplement include but are not limited to the following types of changes if they affect the safety or effectiveness of the device:
>
> (1) New indications for use of the device,
> (2) Labeling changes,
> (3) The use of a different facility or establishment to manufacture, process, or package the device,
> (4) Changes in manufacturing facilities or quality control procedures,
> (5) Changes in sterilization procedures
> (6) Changes in packaging,
> (7) Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device,
> (8) Extension of the expiration date of the device based on data obtained under a new or revised stability or sterility testing protocol that has not been approved by FDA.

The key issue here is that the preceding types of changes must be the subject of a PMA supplement only if the change affects the safety or effectiveness of the device. Thus, for changes such as those named in the regulations, the applicant has the burden of determining whether a change impacts safety or effectiveness. If, however, the applicant can determine that a particular change enhances the safety of a device, a "Special PMA Supplement- Changes Being Effected" may be the appropriate mechanism for notification of FDA of the change. Section 814.39(d) addresses changes to devices that enhance the safety of the device or the safety in the use of the device. The regulation provides some examples of the types of changes that enhance the safety of a device. These include, but are not limited to, the following:

> (1) Labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction.
> (2) Labeling changes that add or strengthen an instruction that is intended to enhance the safe use of the device
> (3) Labeling changes that delete misleading, false, or unsupported indications.
> (4) Changes in quality controls or manufacturing process that add a new specification or test method or otherwise provide additional assurance of purity, identity, strength, or reliability of the device.

A "Special PMA Supplement- Changes Being Effected" allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement- Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved should agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Finally, the guidance relies on the applicant to determine when a particular proposed change to a class III device (subject to an approved PMA) does not affect the safety or effectiveness of a device. A determination by the applicant that a proposed change does not affect the safety or effectiveness of a device may either be submitted in an annual report, if called for by FDA, or may simply be documented in the applicant's records. The "document for file" indicates that the applicant has documented the decision making process through the use of this guidance and accompanying flow charts, has generated any data or information appropriate to support that decision, and has reached a conclusion that the proposed change does not affect the safety or effectiveness of the device.

DEVICE CHANGES AND THE QUALITY SYSTEM REGULATION

Any guidance on changes to a marketed device must consider the role current good manufacturing practice requirements play in making the changes. The Agency believes that applicants complying with the Quality System regulation should have in place adequate systems and controls to assure the continued safety and effectiveness of the changed device, and for certain types of changes this may be adequate assurance.

On June 1, 1997, the first revision since 1978 to device good manufacturing practice requirements went into effect. The new regulation, entitled the Quality System Regulation, is of particular significance in any consideration of design changes because it incorporates requirements for

design controls for medical devices (see 21 CFR 820.30(a)). Of equal importance in considering device changes are the provisions strengthening previous good manufacturing practice controls over design and manufacturing changes, and other changes to a legally marketed device.

The Quality System Regulation requires that an applicant have in place a system to document and assess design changes including changes to the manufacturing process of a device, changes to quality control testing, changes to device labeling, and changes that are made to correct or prevent a problem that is identified with a device. Part of the assessment for all changes includes validation or where appropriate verification of changes to the design and processes. Because FDA recognizes the significance and importance of the new Quality System regulation and the extent to which applicants that comply with the requirements of the regulation will have control over device changes, FDA intends to place more reliance on the Quality System Regulation design control requirements to assure the safety and effectiveness of a modified device that is the subject of an approved PMA.

Premarket approval applications typically contain a great deal of detailed information about the manufacturing process for a device. This information includes details of the manufacturing site and process, along with information on methods used for validation of device design, verification of device performance, and validation of device manufacturing processes. FDA dedicates considerable time to the review of the manufacturing section of a premarket approval application, in order to assure that the applicant has systems and controls in place that will help to assure the safety and effectiveness of the device that is being produced. Many of the processes and procedures contained in the manufacturing section of the PMA likewise will be used by the applicant for assessing planned modifications to the device.

Because the applicant and FDA have reviewed and assured the adequacy of these processes and procedures via the original premarket approval application or a previous PMA supplement, the use of the same processes and procedures in the assessment of modifications may yield meaningful data concerning the safety and effectiveness of a device. If, of course, there are more recent guidances or standards recognized by FDA that are applicable to the device, different or additional testing may be indicated. It is the responsibility of the applicant, however, to stay current on accepted test methods and to assure that if a more current method has supplanted earlier accepted methods (e.g. for biocompatibility testing), the more current method is followed.

If the applicant has an acceptable Quality System in place and has followed its own reviewed and accepted processes and procedures, FDA believes it typically can rely on the data that is generated concerning device safety and effectiveness. Under these circumstances, FDA may be able to perform a less detailed review of a PMA supplement prior to implementation of the change and may rely on other forms of notification or documentation.

SCOPE OF THIS GUIDANCE

This guidance document has been developed to aid applicants of class III devices (subject to approved premarket approval applications) who intend to modify their device and are in the process of deciding what type of documentation and/or submission will be necessary for that modification. This guidance for changes to an existing device is intended to supplement the other guidances on premarket approval contained in the ODE Bluebook memoranda on the premarket approval process.

This document was developed to address modifications to device design, device labeling, device materials, and the device manufacturing process other than those governed by 515(d)(6) of the act. This guidance also can be applied to situations when a legally marketed device is the subject of a recall and a change is indicated to assure the safety and effectiveness of the device. This guidance is not intended to apply to combination products such as drug/device or biologic/device combinations. During PMA review for a new drug/device combination or biologic/device combination, the sponsor and FDA should discuss and determine which aspects of this guidance, if any, apply.

Furthermore, this guidance is not intended to address the need for submitting a PMA when potential applicants who are not the holders of the PMA make changes in a marketed class III device subject to PMA requirements. For purposes of this document, however, the term applicant includes any holder of an approved premarket approval application, whether or not that individual actually manufactures the device in question.

The purpose of this guidance is to help the applicant determine when a PMA supplement or other notification to FDA is required. It does not address how to test devices to determine the effects of changes. Under the Quality System regulation, applicants are responsible for determining the tests that must be performed and documentation that must be prepared in assessing the effects of any change to a device.

This guidance is not intended to supplant existing device specific guidance. Wherever device specific guidance exists, it generally will should be applied to the device unless it is not consistent with the current requirements of the regulations or act.

This guidance incorporates three separate flowcharts for *in vitro* diagnostic devices (IVDs). These flowcharts cover changes in technology or performance, change assessment, and materials changes for IVDs. This draft guidance applies to in vitro diagnostic devices regulated by the Center for Devices and Radiological Health and is may or may not apply to in vitro diagnostic devices regulated under premarket approval by the Center for Biologics Evaluation and Research (CBER).

ASSUMPTIONS

In developing this guidance for aiding decisions about when a PMA supplement is required prior to marketing a modified product, a number of assumptions were made. Thus, anyone using this guidance needs to bear in mind the following assumptions:

- The guidance should be applied to the intended changes to devices and not to any unforeseen results of implementing a change that may be discovered during design validation. It is important, however, to remember that such unforeseen results may affect safety or effectiveness and, thus, may be key in deciding whether to submit a PMA supplement.

- Because many changes occur in the evolution of a device, each change must be assessed individually, as well as collectively with other changes made since the last PMA supplement. When the effect of one change, considered together with a previous change or changes to a device, leads an applicant to submit a PMA supplement, information on the relevant cumulative changes should be included in the supplement in order for FDA to fully assess the safety and effectiveness of the modified device.

- Whenever an applicant changes a device, the applicant must comply with the Quality System regulation. This regulation requires that changes to devices be subject to controls and that the more significant the change, the greater the likelihood that the controls will be as stringent as those applied to the original device. If the change applies to the device design then the same controls that applied during the design must apply. Documentation of the controls in place, data from validation and verification activities, records of testing, analysis, and the decision-making process will help to support the applicant's decision that a PMA supplement is not required. Alternatively, this documentation may be a required part of a PMA supplement or special supplement.

- An applicant should have in place a process for evaluating changes to devices subject to premarket approval requirements that incorporate the decision-making processes specified in this guidance, or another acceptable alternative decision-making process. This will help assure consistency and uniformity in the way decisions are made and thus will help to assure correct decisions.

- For changes resulting from a recall or corrective action, FDA believes that, when appropriate and possible, real time or interactive review should be available in order to assure a continued supply of safe and effective devices. There will be other instances where real-time, expedited review or interactive review is appropriate as well. An applicant who believes a particular submission is an appropriate candidate for real-time review should indicate this in a cover letter in submission, along with supporting rationale. Applicants should understand that many factors influence FDA's ability to provide real-time review, including resource constraints, availability of the appropriate representative/s of the applicant, information provided, type of device involved, type of change, etc. FDA will make an effort to provide real time review whenever appropriate.

- This guidance cannot address every type of change for every type of device. No matter how carefully the guidance is applied, there will still be decisions in a "gray area" that applicants will have to make. Applicants may contact the Office of Device Evaluation of these instances, to discuss the proposed change and receive further guidance. Based on the experience gained from these discussions, this guidance may be refined to better reflect the universe of medical device modifications.

- Applicants should understand that there may be instances where use of this guidance suggests that a PMA supplement should be submitted to FDA, but, in fact, FDA may require an original PMA to be submitted. Some changes to a device may be such a departure from the original device or may so significantly impact the safety or effectiveness of a device that only through review of an original PMA can the safety, effectiveness, and clinical usefulness of the device be assured.

- This guidance identifies some specific areas where an applicant's adherence to a recognized test method, standard, or guidance, or to an FDA approved protocol provides a different reporting mechanism. FDA encourages applicants to identify additional areas where FDA would have the opportunity to review and approve a protocol addressing testing requirements for other types of changes and to discuss with FDA the possibility of including these protocols in an original PMA or PMA supplement in order to potentially accelerate the review process for additional changes.

- Applicants should assess each change or each series of changes in accordance with all appropriate pathways shown in the flowchart. For example, a change in environmental specifications or performance characteristics for a device may also necessitate a change in device labeling. Such changes should be assessed using each of the flowcharts that is applicable and the applicant should select, as the appropriate type of submission or documentation, the most stringent result reached.

- This guidance is intended only to assist applicants in determining whether a PMA supplement should be submitted. It does not address review time, determination of requirements for panel review of PMA supplements, or other aspects of PMA or supplement review process.

THE MODEL

The model uses a series of flowcharts to help the applicant through the logic scheme necessary to arrive at a decision on whether to submit a PMA supplement for a change to a device. These flowcharts cover the major types of changes or reasons for making changes to an existing device. The flowcharts cover all devices, including in vitro diagnostic devices (IVDs); there are some additional flowcharts specific for IVDs. Although the same general regulations apply to all devices

including IVDs, there are some regulations that are specific to IVDs, for example, labeling regulations in 21 CFR 809.10. In addition, the unique characteristics of IVDs must be taken into consideration in making certain decisions about the need for PMA supplements.

The flowcharts include:

- Changes due to recalls and corrective actions
- Labeling Changes
- Technology or Performance Changes
- Technology or Performance Changes Specific for IVDs
- Change Assessment for Devices
- Change Assessment Specific for IVDs
- Packaging/Sterilization Changes
- Materials Changes for Devices
- Materials Changes Specific for IVDs

The user is referred to the Definitions section for the meaning of terms used in the flow charts.

To use the flowcharts properly, applicants should answer the questions posed in the flowcharts for each individual type of change, e.g. technology change, material change, etc., until a decision is made either to consider submitting a PMA supplement, "Special PMA Supplement-Changes Being Effected," an annual (or periodic) report, or to document the decision in design control or other appropriate files. It also is important to review the flowchart for all changes or reasons for change that apply to a single device modification and to select the most stringent result that is reached. For example, the applicant may make a labeling change to reflect a change in dimensional specifications. Both the flowcharts for labeling changes and technology or performance changes must be followed through in order to determine the appropriate decision regarding submission of a PMA supplement.

If an applicants' consideration of all planned changes results in a decision merely to document the change and decision-making process and rationale, all necessary data and records should be included with or referenced by the documentation. The applicant should also comply with any other applicable requirements of the Quality System regulations.

It is important to be aware that this guidance is not prescriptive, but is intended as an aid in the assessment of changes to devices subject to an approved PMA. If the applicant believes the decision reached may not be appropriate, s/he is encouraged to contact the Office of Device Evaluation to discuss the change and the conclusion. This also is an appropriate route for those circumstances where the proposed change or changes are not addressed in either the flowcharts or in device specific guidance.

Not all questions contained in the flowcharts apply to all devices. For example, question C1.8 asks whether there has been a change to software or firmware. If assessing a change to an electromechanical device which does not incorporate or use software or firmware, simply answer the question "no" or "not applicable" and move on to the next applicable question.

Note that the flowchart, unlike the 510(k) flowchart, incorporates changes to legally marketed devices that result from a recall or corrective action. These changes are addressed first in the flowchart because of their importance to the safety and effectiveness of devices and because FDA intends, wherever possible and appropriate, to give priority to the review of these changes in order to assure a continued supply of safe and effective devices.

Each of the questions listed on the detailed flowcharts are identified by the flowchart letter (A-D) and a sequential number. The flowcharts for devices and IVDs are identified by name. Those questions on the main spine of the flowcharts relate to major questions to be asked and are identified by a letter and a number, such as A1, A2, etc. Subsidiary questions that are asked in response to a "yes" answer are identified by the same letter, a number denoting the flowchart and a second number denoting the question. For example, C2.1 in Figure C2 labels a decision point

containing the question “Is the Change Designed to Improve Safety Based on Clinical Experience?” which follows a “yes” answer to the question in C1.8 whether there has been a change to software or firmware.

CHART A - CHANGES DUE TO RECALLS AND FIELD CORRECTIVE ACTIONS

Chart A illustrates the logic scheme to be used when determining whether a PMA supplement is required for a change resulting from a recall or field corrective action.

Note that not all recalls require PMA supplements. For example, a simple labeling/manufacturing mix-up resulting in the wrong product being put in the wrong package can be corrected without any change to device design, performance, manufacturing process, labeling, etc. For these types of problems leading to recall, use of this chart may not be necessary or appropriate.

Any change that is needed to a marketed device in order to correct a problem that exists in the field or to assure a continued supply of safe and effective devices will receive, whenever possible and appropriate, expedited or interactive review.

A1 Is the change due to a recall or field corrective action?
A “yes” answer indicates that a device is being changed due to a problem identified after the device has left the applicant’s control and that there may be a user or patient population at risk. Go to A2. If the answer is “no,” go to Chart B.

A2 Is the proposed change a change in the design of the device?
If the change is a design change, the key issue, is whether the device continues to meet its original specifications? [Note: The specifications that are referred to here are performance specifications as defined in the definitions section. This question does not refer to process specifications, which include manufacturing process specifications and in-process device specifications, component specifications, production environmental specifications, or equipment specifications. These changes are assessed under Chart C.] A PMA supplement is required. Because the change is due to a recall or field corrective action, the supplement may qualify for expedited review.

A3 Is the proposed change a labeling change?
If the answer is “yes,” the applicant is referred to the labeling chart to determine the type of supplement required. Note that if the outcome of this review is a PMA supplement, the supplement may be an appropriate candidate for expedited or interactive review.

A4 Is the proposed change the addition of a quality assurance inspection step?
If the proposed change to the recalled device to eliminate the problem that resulted in the recall is the addition of a quality assurance step during the manufacturing process, the applicant may submit a special PMA supplement for a change being effected.

A5 Is the proposed change a manufacturing change to meet the original approved specifications for the device?
If the manufacturing process is being changed in order for the device to meet its original approved specifications, the applicant may submit a special PMA supplement for a change being effected.

A6 Is the proposed change a change to the sterilization process or to device packaging?
If the sterilization site or process or the device packaging is to be changed with respect to the recalled device, go to Chart C3, step 3.1. Chart C3 is applicable to all devices. Again, note that for decisions resulting from the use of Chart C3 for recalled devices or devices subject to field corrective action that conclude in a determination that a PMA supplement is the recommended route, FDA will consider these supplements for expedited or interactive review as appropriate.

A7 Is the proposed change a materials change?
If "yes", go to Chart D or Chart IVD-D for in vitro diagnostic devices. Once again, if the result of following the decision pathway in those charts for a recalled device is that a PMA supplement is the recommended route for submission, FDA will consider such a supplement for expedited or interactive review as appropriate.

If the response to question A7 is "no," the conclusion is drawn that the device is not being reintroduced to the market. Should this be an incorrect conclusion, immediate contact with the FDA reviewing branch and the Office of Compliance is indicated.

CHART B - LABELING CHANGES

Labeling changes are handled with a separate logic scheme that focuses on changes in indications for use, certain changes in instructions for use, changes to performance claims, and removal of warnings, precautions, or contraindications as the triggers for submission of a PMA supplement. Other types of changes to labeling are recommended for other types of submissions or for documentation.

Chart B describes the logic scheme to be used when determining when a PMA supplement or other submission is required for a labeling change for devices. When dealing with class III devices, the agency is interested in reviewing many types of labeling changes, since they may have a significant impact on the safe and effective use of a device.

B1 Revisions for Clarity or Ease of Use?
Labeling changes may result simply from a desire on the part of the applicant to provide more detailed or explicit directions for users or to respond to frequently-asked questions from customers. A "yes" answer to this question indicates that the only reason for the labeling change was to provide clarity and that the change did not result from the need to prevent erroneous use or misapplication of a device. An example of a labeling change for clarification is a user instruction that previously stated the top of a device should be placed facing upward; the revised instruction would state that the pebbly surface of the device should be placed facing upward. An IVD example would be an instruction to perform a test at room temperature that could be clarified by specifying that room temperature is 20-28C.

B2 Affect Instructions for Use?
Adding or deleting instructions for use will require a PMA supplement. Editorial changes to instructions for use can be reported in an annual report.

B3 Affect Indications for Use?
Changes in the indications for use section of labeling typically can only be made based on additional analytical or clinical data demonstrating the safety and effectiveness of the device for an additional indication or population. Thus, most changes in this part of the labeling will require the submission of a PMA supplement.

However, a change in the indications for use that limits use to within the current indications may not require a PMA supplement. An example of this is that a device may have three user populations identified in the indications for use: a geriatric population, a normal adult population, and an infant population. A company may make a decision not to market a device for an infant population based solely on legal issues or limitations in the distribution network for the device. If, however, such a decision were made based on problems encountered with the device in a portion of its intended user population, a PMA supplement would be required, since this would indicate there was a change in the safety and effectiveness of the device for its original intended use. Any expansion in the indications for use would, of course, require a PMA supplement.

Note that a change in the intended use of a device would always require either a PMA supplement or a new original PMA submission.

B4 Add or Strengthen Warning, Precaution, Contraindication?
Additions to the labeling of warnings, precautions, and contraindications are made typically as a result of monitoring device usage and adding information based on user experience. Events that precipitate changes of this type for class III devices are often identified and reported through the medical device reporting regulation (MDR) 21 CFR Part 803. For example, new types of adverse events that are added to labeling are considered "strengthening a warning."

While a PMA supplement is required for such a change, due to the fact that important new public health information is involved, FDA is encouraging applicants to make these types of changes promptly and prefers to review a special PMA supplement for changes being effected. In this way, users and patients will have access to important new information promptly and FDA will have an opportunity to review the information and, if necessary, to obtain additional information either before or after the change goes into effect.

B5 Delete warning, precaution, contraindication?
A desire by the applicant to delete a warning, precaution, or contraindication typically indicates that additional analytical or clinical data has been generated that shows the warning, precaution, or contraindication is not required. In such a case since the placement in the labeling was based on data and/or experience, FDA wants to review a PMA supplement prior to the removal of this information.

B6 Change to performance claims?
Like changes in indications for use, a change to performance claims for a device can only be made if the applicant has generated additional data or information on the safety and effectiveness of the device in question. In this case, FDA wants the opportunity to review that data or information as part of a PMA supplement prior to the applicant changing performance claims for its device.

For IVDs, various types of labeling changes that should be evaluated to determine their impact on performance claims include changes in the conditions of specimen collection, transport, or storage, changes in test procedure or test conditions, and changes in the method of data analysis and reporting. These types of changes must be carefully evaluated by the applicant, typically through analytical or clinical studies, which provide information on performance characteristics of the IVD. If the conclusion is that the change in labeling does not represent a change in performance claims for the IVD, both the rationale for the decision and the supporting data must be documented.

CHART C-TECHNOLOGY OR PERFORMANCE CHANGE

Chart C covers a variety of types of changes in technology or performance of medical devices. If the proposed change is a technology or performance change of the types detailed on the chart and the device is not an IVD, proceed to question C1.0. If the device is an IVD, go to chart IVD-C1, which is discussed following this section.

C1.0 Is the proposed change a change in the manufacturing site for the device?
A change to the manufacturing site specified for the device in the approved PMA or a subsequent approved supplement requires a PMA supplement.

C1.1 Is the proposed change a change in the control mechanism for the device?
Almost all changes in the control mechanism for a device raise questions of safety and effectiveness and therefore will require the submission of a PMA supplement. One example of a control mechanism change for a device is a change from analog to digital control. A change to digital control may markedly improve device performance specifications and effectiveness and often necessitates a major redesign of the device. Another example of a change in control mechanism would be a change from pneumatic to electronic control for a respiratory care device. It should be noted that not all devices have a control mechanism, e.g. inactive medical devices such as certain orthopedic implants.

C1.2 Is the proposed change a change in operating principle?
Like a change in control mechanism, a change in operating principle typically involves major redesign of a device and generation of preclinical and clinical data to determine whether safety or effectiveness are enhanced by the change. Thus, a PMA supplement usually is the appropriate route for submission.

An example of a change in operating principle for a device is a change from a manual to a software driven device. Some changes of this nature will also be captured under labeling changes and should be evaluated in accordance with both applicable charts to determine the appropriate pathway. Also note that some minor changes in operating principle, e.g. a minor change to an algorithm, may readily be validated by the applicant in accordance with the Quality System regulation and thus, may not require a PMA supplement. See C1.8, below.

C1.3 Is the proposed change a change in energy type?
Often a change in energy type requires a PMA supplement, because the change may enable the use of the device in a different environment or at a different location than the original device. Changes in energy type may also give rise to significantly different operating characteristics for the device and, accordingly, may impact the device's safety or effectiveness. A change of this type also could be expected to be accompanied by significant labeling changes.

An example of a change in energy type is a change from AC to battery power. Note that this type of change does not necessarily include all changes in the energy source itself. For example, a change from one type of battery to another may not change the safety or effectiveness of a device and, thus, may not trigger the need for a PMA supplement, this of course depends on the type of device.

C1.4 Is the proposed change a change in environmental specifications?
That is, has the environment in which the device can be used, transported, or stored been changed? See C2.1 below for a discussion of change assessment.

C1.5 Is the proposed change a change in performance specifications?
See "definitions" for a description of performance specifications and see C2.1 below for change assessment.

C1.6 Is the proposed change a change in ergonomics or in the patient/user interface?
An example of a change in ergonomics is a change in patient positioning on a lithotripter table, which may affect the delivery of energy to the patient. A change in patient or user interface is exemplified by the addition of a computer interface for a physician's use in programming of a device. See C2.1 for change assessment.

C1.7 Is the proposed change a change in dimensional specifications?
That is, did the size or shape of the device change? See C2.1 for change assessment.

C1.8 Is the proposed change a change in software or firmware for the device?
See C2.1 for change assessment.

C1.9 Is the proposed change a manufacturing or QA inspection change?
If the proposed change represents a modification of the manufacturing process or changes or additions to or deletion of inspection or testing steps, it also must be evaluated in accordance with Chart C2, Change Assessment for Devices. Changes to the manufacturing process include changes in the manufacturing environment.

Chart C2 - Change Assessment

The types of changes identified at decision points C1.4 through C1.9 represent design or engineering changes or manufacturing process changes (excluding changes to sterilization and/or packaging, which are covered under Chart C3 and material changes, including changes to material formulation, which are covered under Charts D and IVD-D.) They encompass a vast number of changes from routine specification changes designed to maintain device performance to significant product redesign.

The logic scheme that is detailed below is intended to assist applicants in determining whether a particular change identified by C1.4 through C1.9 is likely to be significant enough to affect the safety or effectiveness of the device and thus trigger the requirement for a PMA supplement. Changes to performance specifications, dimensional specifications, or software/firmware that do not trigger the requirement for a PMA supplement are to be included in an annual report, while changes to environmental specifications, changes to ergonomics or patient/use interface, or changes to manufacturing or QA inspections are to be documented for the file, as indicated in the flowchart.

C2.1 Is the change designed to improve safety based on clinical experience?
Any time there is a change to improve safety, a PMA supplement is required. A "yes" answer leads to a decision to submit a PMA supplement, because changes that are intended to improve device safety and for which clinical experience has shown the need for safety improvement are of significant interest to FDA. A PMA supplement proposing an improvement to device safety may be a candidate for expedited or interactive review. A "no" answer to this question indicates that the change did not address safety.

C2.2 Does the proposed change affect the indications for use?
This question does not ask specifically whether the indications for use were changed, but only if the change affects the indications for use, for example, by creating an implied new indication for use. A device could be modified in order to enable a new use, even though the new use might not appear in device labeling. For example, a change to the software of an excimer laser might permit additional uses of the device. If the answer to this question is "yes," a PMA supplement is required.

C2.3 Is clinical data needed to establish that the device is safe and effective?
If the answer is "yes," a PMA supplement is required. If the device can be shown to be safe and effective without the generation of clinical data, the response to this question is "no." In the latter case, if the response is clinical data is not needed to establish device safety or effectiveness, safety and effectiveness may be assessed through, for example, animal testing, bench testing or simulations.

C2.4 Is the change qualified to the original specifications through an FDA recognized test, standard, or guidance?
This question does not address new assessment methods, but new or changed technology or performance. For changes not impacting safety and not requiring clinical data to establish safety or effectiveness or conformance to a recognized standard, the response to this question may provide an alternative to a PMA supplement.

In order to use an alternative route, the change must be qualified to the specification contained in the original PMA or a subsequently approved supplement or there must be a test, standard, or guidance recognized by FDA as appropriate for qualification of the particular type of change. The test method, standard, or guidance would have to have been specified in the original PMA or in a subsequently approved supplement and there must be established pass/fail criteria. If FDA has already determined that the methodology is appropriate for assessment of certain types of changes, then a change to the device which results in the device continuing to meet that test requirement may not require prior review and approval by FDA. If additional tests are needed to

establish safety or effectiveness, a PMA supplement must be submitted. If a new test is simply confirmatory, submission is not automatically required. If such a test, standard, or guidance does not exist, the answer to this question is "no" and a PMA supplement is required.

It is important that the applicant remain current on test methodologies and if the testing performed in the original PMA does not represent the current industry standard or FDA recognized method, the most current accepted method should be used.

C2.5 Are new safety and/or effectiveness issues raised by testing?
Testing can include either clinical or preclinical testing. If, during testing, data or information is developed that was not within the original design of the device, new safety or effectiveness issues may be raised. For example, if the device no longer meets its original or current specifications and new issues of safety or effectiveness are raised, the answer to this question is "yes." This response leads to a decision to submit a PMA supplement.

On the other hand, if changes to device design or manufacturing processes are validated and/or evaluated according to an approved protocol to assure that the device continues to perform as intended and meet its original or current specifications, documentation of results and inclusion either in an annual report or a document to file typically will be sufficient.

An example of the analysis required under this section is for dimensional changes in mechanical heart valves. If a manufacturing change is made which tightens up the dimensional tolerance (C1.7) of the fit between the housing and leaflets, the regurgitation volume may go down. The heart valve will meet the original regurgitation specifications. However, there may be a new safety issue raised in terms of cavitation that would require additional testing (C2.5), via a new test method. This change would require a PMA supplement.

C2.6 Change in a manufacturing method or procedure?
If the change affects safety and effectiveness and is not a manufacturing change in method or procedure, then a PMA supplement is required. If the change is a manufacturing change in method or procedure, affects safety and effectiveness, and is made in compliance with GMP requirements, then the holder of the approved application may submit a detailed notice thirty days prior to marketing the device (Section 205 of the FDA Modernization Act of 1997). The written notice should describe the change in detail, summarize the data or information supporting the change, and certify compliance with GMPs. During the thirty day window, the agency may inform the holder of the approved application that a supplement is necessary, based upon the information in the notice. (Note that changes in manufacturing methods or procedures that do not affect safety and effectiveness are to be documented for the file, as indicated in the flow chart.)

CHART IVD-C1 - TECHNOLOGY OR PERFORMANCE CHANGE FOR IVDs

The flowchart for IVD decision-making captures only those questions that are relevant to in vitro diagnostic devices. Some of these are similar to the questions that are asked for medical devices, while others are specific to the operating characteristics of IVDs.

IVD-C1.0 Is the proposed change a change in manufacturing site?
If the IVD will be manufactured at a site other than the site specified in the approved PMA or subsequent approved supplement, submission of a PMA supplement is required.

IVD-C1.1 Is the proposed change a change in the operating principle for the IVD?
A change in operating principle for an IVD is a change in the basic technology used in the assay or a change in the mechanism of operation used in an IVD instrument (e.g. automated PAP smear screening device.) For example, a change from radioimmunoassay to enzyme immunoassay is a change in operating principle, as is a change from ELISA to amplified probes. If the answer is "yes," a PMA supplement is required.

IVD-C1.2 Is the proposed change a change in specimen collection, transport, or storage? Changes in the method of collection, transport, or storage of patient specimens for IVD testing are evaluated in accordance with Chart IVD-C2 for changes.

IVD-C1.3 Is the proposed change a change in test procedure or format?
Examples of changes in test procedure include such things as addition or deletion of testing steps, changes in incubation temperatures, changes in the time required to perform the test, and changes in the method of data analysis or reporting. Changes in test format include addition or deletion of reagents, change in the container, surface, or substrate upon which the test reaction takes place, and changes in sizes or concentrations of reagents (e.g. changing from a liquid to a lyophilized reagent). These changes are evaluated in accordance with Chart IVD-C2 for changes.

IVD-C1.4 Is the proposed change a change in the instrument hardware upon which the test is performed or read?
Most instruments used to read the results of IVD assays are covered by 510(k), even if the specific reagents are considered a PMA device. There are a few IVD instruments, however, that are PMA devices, such as automated PAP smear screening devices as mentioned above. This guidance applies only to IVD instruments that are the subject of a PMA. Changes to these instrument are evaluated by referring to Chart IVD-C2.

IVD-C1.5 Is the proposed change a change in software or firmware?
Software/firmware may be used to run a diagnostic assay or to analyze data and report results. The majority of instruments currently used to perform IVD assays are reviewed via premarket notification. If, however, an IVD instrument is covered by a PMA submission, these changes are evaluated in accordance with Chart IVD-C2.

IVD-C1.6 Is the proposed change a change in manufacturing or QA inspection?
Changes in the manufacturing process (equipment, procedures) or QA inspection or test procedures are evaluated in accordance with Chart IVD-C2.

If the changes listed in IVD-C1.0 through IVD-C1.6 do not describe the proposed change, the applicant should proceed to Chart C3 for changes to packaging or sterilization and to Chart IVD-D for material changes.

Chart IVD-C2 - Change Assessment for IVDs

Chart IVD-C2 contains the questions for change assessment for the changes listed in IVD-C1.2 through IVD-C1.6.

IVD-C2.1 Does the proposed change affect the indications for use of the IVD?
Please note that these types of changes are not limited to changes in the claimed indications for use (these would be captured under labeling changes), but include changes which, by their nature, suggest new indications for the IVD. If the proposed change affects the indications for use, the answer to this question is “yes,” and a PMA supplement is the appropriate route for marketing.

IVD-C2.2 Does the proposed change alter the performance characteristics of the IVD?
As noted above, this assessment is not limited to whether the performance claims made for the IVD are changed (this change would be captured under labeling changes), but also covers actual changes to performance characteristics, e.g. sensitivity, specificity. The types of changes that merit strong consideration for submission of a PMA supplement are those detailed in 21 CFR 809.10(b)(7), (9), (11), (12). If these types of changes result in changes in the performance characteristics of the IVD, a PMA supplement is required.

If the proposed changes listed in IVD-C1.2 through IVD-C1.6 do not generate “yes” responses to any of the questions posed, changes in specimen collection, transport, or storage and changes in test procedure or format may be documented in the annual report. Changes in instrumentation, software or firmware, or manufacturing/QA inspection can be documented in an annual report.

CHART C3 - PACKAGING/STERILIZATION CHANGES

Chart C3 applies to both medical devices and IVDs. It provides a logic scheme for the assessment of changes in packaging or sterilization processes.

C3.1 Is the device (or IVD) sterile?
If yes, proceed to question C3.1.1. If no, proceed to question C3.10.

C3.10 Is the proposed change a change in packaging for a nonsterile device?
This question addresses all device packaging, as defined in the definitions section of this document.

C3.10.1 Was the proposed change in packaging to the nonsterile device validated according to an approved protocol to assure that packaging conforms to the original or current specifications for the packaging?
If the response to this question is "yes," documentation for the file is recommended. If "no," proceed to C3.1.4.

C3.1.4 Did testing conform to a recognized standard or guidance?
If the testing of the packaging was not validated to the original or current specifications, if testing conformed to a recognized standard or guidance, the change to packaging could be reported in an annual report. If not, a PMA supplement should be submitted.

C3.11 Is the proposed change a change to the expiration date for a nonsterile device?
If not, the change should be documented for file. If yes, proceed to question C3.12.

C3.12 Is the expiration date being changed in accordance with an FDA approved protocol?
If FDA has reviewed and accepted a protocol for changes to the expiration date and testing was performed in accordance with that protocol, the change to the expiration date can be made and reported in an annual report. If not, a PMA supplement should be submitted.

C3.1.1 Is the proposed change a change in packaging for a sterile device?
Where "packaging" is defined in the definitions section of this document. If the answer to this question is "yes," follow the flowchart for both packaging changes (C3.1.2) and any other changes that may apply (Sterilization site C3.2, Sterilization method C3.3, Change within Existing sterilization method C3.4, change to expiration date C3.5)

C3.1.2. Is the proposed change a change in the sterile or primary package for a sterile device?
If the response is "no," the other packaging for a sterile device is assessed in accordance with the logic scheme for changes in packaging for nonsterile devices (i.e. see C10.1 and C3.1.4, above).

C3.1.3 Is the proposed change in the sterile or primary package for a sterile device validated to the original or current packaging specifications through an FDA approved protocol?
If the sterile packaging for a sterile device is validated to original specification, package integrity and product sterility must be considered and must be a part of the device specifications. If the answer to this question is "yes," the information can be reported in an annual report. If "no," see C3.1.4., above.

C3.2 Is the proposed change a change to the sterilization site for the device?
If so, FDA has an interest in determining the compliance of the proposed site to good manufacturing practice requirements.

C3.2.1 Is the proposed new sterilization site registered with and inspected by FDA as a sterilization site?
In order to answer this question "yes," the previous inspection of the site must have been classified by FDA as anything other than "OAI." If "yes", go to C3.3. If "no" or if the previous inspection was classified as "OAI", a PMA supplement is required, providing FDA notice and opportunity to inspect the site prior to approving the change.

C3.3 Is the proposed change a change in sterilization method?
A change to the sterilization method indicates a method that is different than that originally approved for the device in the PMA or a subsequently approved supplement. Even if the sterilization method was approved for a different device made by the same manufacturer or for the same device manufactured by a different manufacturer, a change to the sterilization method approved for this specific device is the one that must be assessed. Changes within a sterilization process have the potential for changing performance characteristics of the device. When applicants make changes within or between sterilization methods, it is important to document the impact on properties or specifications of a device to assure they remain unchanged. Examples of changes in sterilization method are a change from EtO to gamma irradiation, or a change from filtration to steam sterilization. If "yes," a PMA supplement is required in order to permit FDA to review the details of the new sterilization method and its validation.

C3.4 Is the proposed change a change within the existing sterilization method?
Examples of changes within an existing sterilization method include a change in the Sterility Assurance Level (SAL) of the finished product, a modification to the sterilization process such as load configuration, or a change in process parameters. If "yes," proceed to C3.7, below.

C3.5 Is the proposed change a change to the expiration date?
If not, and if the answers to the preceding questions have been no, documentation for the file may be sufficient.

C3.6 If there is a change to the expiration date, is there an FDA approved protocol for shelf-life extensions?
The FDA approved protocol for shelf-life extensions will include the data that must be generated for the device, so that an assessment of changes to the device can be made. If the answer to this question is "yes," the change can be reported in an annual report. If there is no FDA approved protocol, a PMA supplement should be submitted.

C3.7 Is there a change to device performance specifications or a decrease in SAL?
If there has been a change within the existing sterilization method and that change affects device performance specifications or results in a decrease in the SAL for the device, a PMA supplement is required. It should also be noted that an increase in SAL may have an impact on the device itself, such as a change in material properties.

For example, an increase in the SAL may require a more rigorous sterilization cycle that may have a harmful effect on certain materials. Certain plastics are especially susceptible to radiation doses commonly used for sterilization and some materials of biological origin and plastics are susceptible to ethylene oxide.

C3.8 Was the device validated to its original or current specifications?
This question can be applied to sterile products. If there is a proposed change within the existing sterilization method that will not change device performance specifications or decrease the SAL of the original device and the device was validated to its original or current specifications, the change can be implemented and reported in an annual report. If not validated to its original or current specifications, a PMA supplement is required.

CHART D - MATERIALS CHANGE FOR A DEVICE

Changes in materials often engender additional changes in a device, such as a change in labeling or a change in performance. These additional changes, if they occur, would already have been considered through the use of this logic scheme. Bear in mind that the applicant should follow the flowcharts for any applicable change that would result from a particular type of change and should apply the most stringent result that is reached.

D1 Is the device an IVD?
If the device is an IVD, the applicant should refer to the flowchart for IVDs, Chart IVD-D.

D2/3 Is the proposed change a change in material type, source or formulation?
Material types are the generic names of the materials from which a device is manufactured. An example of a change in material type is the change from natural latex rubber to synthetic rubber. Material source does not refer to the vendor from whom the material is purchased, but covers changes in the origin of the material, such as a change from epithelial cells of human origin to epithelial cells of bovine origin (see D8). Material formulation is defined in the definitions section. Changes to material type, source or formulation must be assessed in accordance with the type of device, the type of body contact, the methods used to assess the material change and the result with respect to the finished device.

D4 Is the proposed change a change to material supplier?
If "no," the change can be documented for the files.

D5 Is there a change in material specifications associated with the proposed change in material supplier?
If "yes," the applicant is referred to Chart C2 for Change Assessment. If "no," proceed to D5.1.

D5.1 Will the affected part contact body tissue or fluids?
If "no," the change must be documented to file. Under the Quality System regulation, records would be kept to show there is no change to material specifications. In addition, there are requirements for vendor qualification that must be met. If "yes," continue to D5.2.

D5.2 Does the material conform to a standard?
If "yes," the change must be documented to file. Examples of applicable standards would be ASTM standards covering metals such as stainless steel. If "no" proceed to D5.3.

D5.3 Does the device with the new supplier material meet the qualification requirements of the original or current device?
If "no," a PMA Supplement is required. If "yes," proceed to D5.4.

D5.4 Is the device an implant?
If "yes," the change in material supplier must be included in the Annual Report. If "no," the change must be documented to file.

D6 Is the device whose material is changed in type, source, or formulation an implant?
See the definitions section for the definition of an implant. Different assessment pathways are provided for devices that are implants versus devices that are not implants.

D7 If the device is not an implant, will the affected part be likely to contact body tissue or fluids in vivo?
The affected part of the device is the part for which a material change is proposed. If the response is "yes," go to D7.1.

D7.1 Is the changed material of human or other animal origin?
Any change to a material of human or other animal origin that is likely to contact body tissue fluid is a significant change that requires a PMA Supplement.

D8 Is the material qualified to the same biocompatibility tests of the PMA or to updated requirements of ISO 10993-1?
This question must be asked of a non-implant device where the material change affects a part that contacts body tissue or fluid. If the material is qualified to the same test and test requirements as the current PMA, a PMA supplement may not be required. However, the state of the art for biocompatibility testing is evolving and the testing in the current PMA may no longer be adequate. It is the applicant's responsibility to be aware of change to the state of the art as well as FDA requirements for biocompatibility testing and conduct additional tests if appropriate. The applicant should consult with FDA if they have questions about the adequacy of the test requirements of the current PMA. If the response to this question is "yes," go to D10. If the material is not qualified to the tests nor meets the requirements of the current PMA and thus additional tests are appropriate, the response is "no" and a PMA Supplement is required.

D9 Does the affected part contact body tissue or fluids?
If the device is an implant and the material change will affect a part of the device that comes in contact with body tissue or fluid, a PMA supplement is required.

D10 Will there be a change in device performance specifications?
This question is relevant in three cases related to material change: for either an implant or a non-implant where the portion of the device whose material is to be changed does not come in contact with body tissue or fluid, or for a non-implant where the part affected by the material change contacts body tissue or fluid but the material is qualified to the same tests and meets the same requirements of the current PMA or additional updated requirements of ISO 10993. If there is no change in device performance specifications, document to file when no contact with body tissue or fluid is involved; include in the annual report when contact is involved. If there is a change in device performance specifications, the change must be assessed by referring to Chart C2.

CHART IVD - D MATERIAL CHANGES FOR IVDs

Because IVDs do not come in contact with the body of a patient and often do not come in contact with the body of the user, the most important considerations for materials changes are the effect of the change on the performance characteristics of the finished product. Some types of materials are more likely to have an effect on performance characteristics and this is reflected in the logic scheme.

IVD-D1 Does the proposed material change result in a change in the performance characteristics of the assay?
If the performance characteristics of the assay are changed, a PMA supplement is required.

IVD-D2 Is the material that is proposed to be changed a reactive ingredient, biological material, or test substrate, container, or surface?
See definitions section for the definitions of reactive ingredient and biological material. The test substrate, container, or surface is the vessel in or on which the assay reaction takes place or the vessel in which the specimen is collected, stored, or transported. These types of changes are changes that have the greatest potential for affecting the performance characteristics of the IVD and the changes about which FDA has the greatest concerns. If such a change does not change the performance characteristics of the assay, it can be reported to FDA in a special PMA supplement for changes being effected. This provides FDA an opportunity to review the change and determine whether additional testing or documentation is required.

IVD-D3 Is the material a catalytic or nonreactive ingredient?
Examples of materials that do not directly participate in an assay reaction are buffers, wash solutions, preservatives, and stabilizers. For changes in these types of materials that do not change the performance characteristics of the IVD, the change can be reported in the annual report.

IVD-D4 Is the material part of an instrument?
As noted previously, most instruments used for IVD assays are covered by 510(k) submissions. For any IVD instrument that is the subject of a PMA, if the material change affects only an instrument used to perform or read the assay and the change does not affect performance characteristics of the assay, the change and supporting documentation may be added to the file.

If the material change does not involve any of the changes noted above, the applicant is referred to Chart C, step C3.1 for packaging to assess the effect of the change.

DEFINITIONS

Annual report: A periodic report in accordance with 21 CFR 814.84

Biological material: A material of animal origin, such as a monoclonal antibody, serum, etc.

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, an applicant may propose a change in method of sterilization. This change could impact on performance specifications because of potential chemical or physical changes to the device. The proposed change in method of sterilization is the change that should be used in the model.

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 electromechanical 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.

Document for File: For the purpose of this guidance, document for file 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: The type of power input to or output from the device. Examples of a change in energy type 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 temperature range in which the device will operate properly or hardening the device to significantly higher levels of electromagnetic interference.

Ergonomic or 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.

Field Corrective Action: A field corrective action is any corrective action taken with respect to a device that has left the direct control of the device applicant. A field corrective action may be required when a device fails to meet its specifications or intended use; it may involve, for example, replacement of defective device parts or components that fail to meet reliability claims or it may involve relabeling of devices.

Implant: A device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also “implants” for purposes of this part.

Intended Use: The words "intended use" refer 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. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.

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." 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,
- clinical laboratory versus point of care versus home use,
- part of the body or type of tissue applied to or interacted with,
- specimen type used for in vitro diagnostics,
- 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, warning, or the bibliography sections. In some instances, a change in the indications for use may imply a change in the intended use for the device.

In vitro diagnostic products (devices) ("IVD"): 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.

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

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. This can include, among other things, any user or maintenance manuals and the intended use, indications for use and claims made for devices in promotional literature.

Manufacturer: A term sometimes used to describe the holder of an approved premarket approval application, whether or not that individual actually manufactures the device in question.

Manufacturing site: For purposes of this document, the manufacturing site of a class III device is any site where any manufacturing operation for that device takes place. Manufacturing operations include design, manufacture, fabrication, assembly, processing, contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development. Note that in this guidance, manufacturing site and site of sterilization are handled separately.

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 materials that are not intended to be part of the finished device. For IVDs, the formulation of a reagent is the quantity, proportion or concentration of each ingredient. Examples of changes in material formulation would be a change from a series 300 stainless steel to a series 400 stainless steel or a change in amount of a preservative used in a reagent.

Material source: The source of a material is its origin. This can include, for biological materials, a change from one species or one body site to another.

Material supplier: The firm supplying raw materials or components to a finished device manufacturer.

Material type: The generic name of the material from which the device is manufactured. 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). Examples of sterilization methods are dry heat, steam, gamma irradiation.

Nonreactive ingredient: A catalytic or nonreactive ingredient is a material or reagent that does not play an active role in a diagnostic assay. Buffers, wash solutions, preservatives, and stabilizers are nonreactive ingredients.

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 the use of a laser rather than a scalpel to ablate tissue. For an IVD, an example would be a change from radioimmunoassay to enzyme immunoassay.

Packaging: Any wrapping, container, etc., used to protect, to preserve the sterility of, or to group medical devices. For IVDs, the containers holding liquid or lyophilized reagents and the pouch holding plates are considered to be packaging; a kit box is not.

Performance Claims: Performance specifications that appear in device labeling or advertising.

Performance Specifications: The performance characteristics of a device as listed in device labeling or in finished product release specifications. Also referred to in the flowchart as performance claims. Some examples of performance specifications for devices are measurement accuracy, output accuracy, energy output level, and stability criteria. Performance specifications for IVDs are the performance characteristics of the assay and not of the individual reagents: examples include accuracy, prevision, specificity, sensitivity, cross-reactivity. They are synonymous with performance claims, because, by regulation, they appear in the labeling for the IVD.

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 includes limitations for IVDs, which are statements of what the assay does not or cannot do. 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. For example, a warning in an IVD package insert might include information on the explosive potential of sodium azide and instructions on proper disposal.
Contraindications describe situations in which the device should not be used because the risk of use clearly outweighs any reasonably foreseeable benefits.

PMA Supplement: A supplemental application to an approved PMA for approval of a change or modification in a class III medical device, including all information submitted with or incorporated by reference therein.

QA Inspection: Any testing or inspection process undertaken to determine whether a material, component, or device meets its established specifications and is safe and effective for its intended use.

Reactive ingredient: A reactive ingredient of an IVD is a material that is involved in the reaction that yields an assay result.

Reagent: An individual component of an in vitro diagnostic assay, usually a chemical or biological material in liquid or lyophilized form.

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.

Recall: A voluntary action taken by an applicant or distributor to remove or correct a product in violation of laws administered by the Food and Drug Administration. Recall includes all actions taken with respect to product that is wholly or partially outside the control of the applicant, whether that product is physically removed to another location for repair, modification, adjustment, labeling, destruction, inspection, or replacement or whether the product is subject to corrective action without its physical removal from its point of use or other location. Products that fail to meet performance specifications or fail to perform as intended, present a risk to the public health, or violate applicable laws or regulations are subject to recall.

Software or firmware: 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, to provide the actions of a medical device, or to analyze data/calculate results from a medical device. This includes firmware that is imbedded or permanently a part of a device and is not modifiable by the user, software that is an accessory to a medical device, or software that is itself a medical device.

Special PMA Supplement-Changes being Effected: A PMA supplement is a supplemental application to an approved PMA that covers a modification or change that enhances the safety of a device or the safety in the use of a device, in accordance with 21 CFR 814.39(d).

Specimen: The sample taken from a patient in order to perform an in vitro diagnostic test procedure.

Sterility Assurance Level (SAL): The level of assurance that a device is sterile. For example, an SAL of 10^{-3} 22 indicates that no more than one nonsterile unit is expected per thousand.

Test format: The test format for an IVD includes the quantities and sizes of reagents, the number of tests that can be performed, the physical location or alignment of materials on a test card or strip.

Test procedure: The test procedure for an IVD includes methods of preparing and reconstituting reagents, steps performed in the test process, order of performance of each step in the test process, length of each step of the test process, temperatures at which the test process is performed, methods of analyzing data and interpreting results.

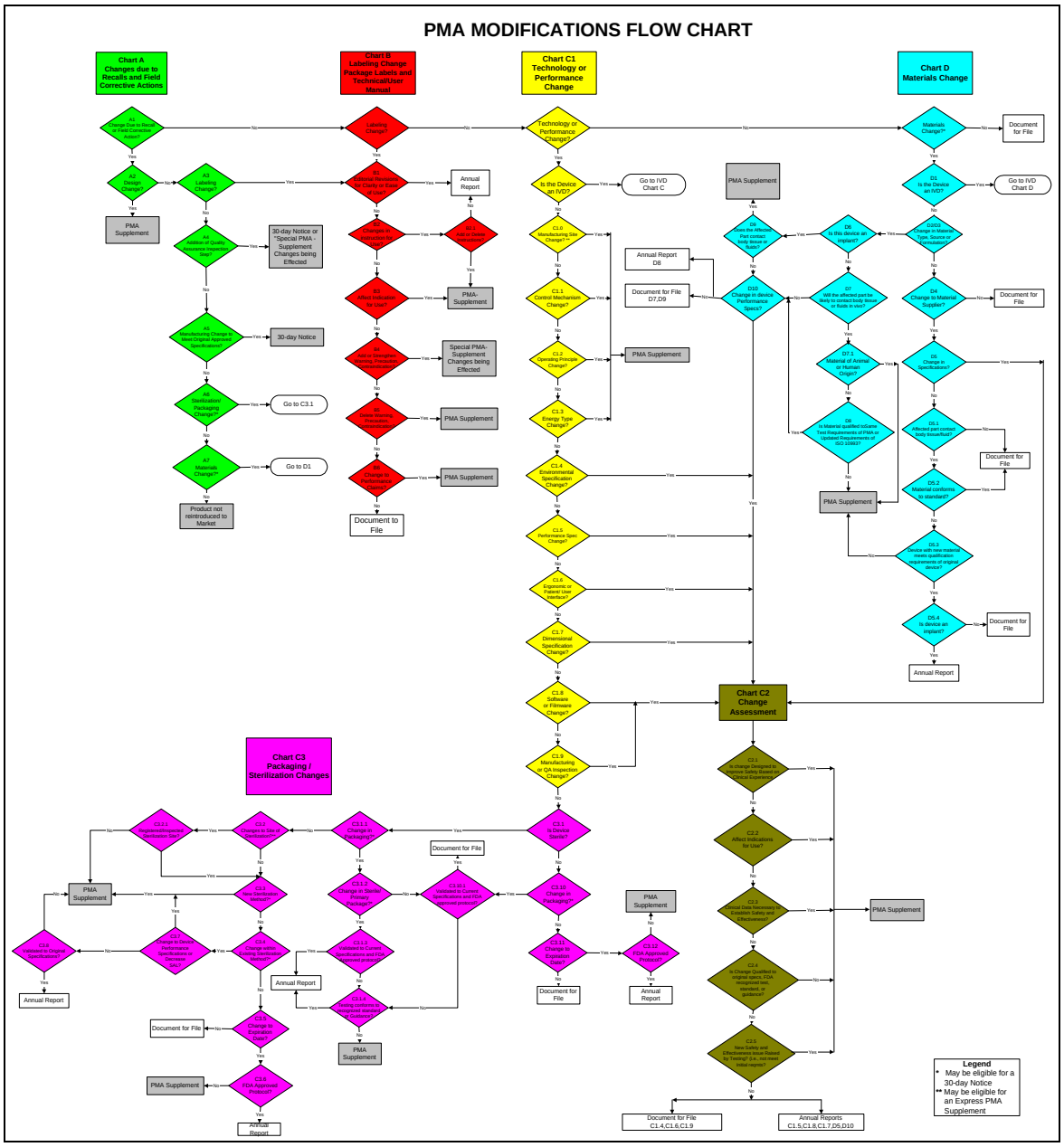
Test substrate, container, or surface: The solid phase on which an assay reaction takes place or the container or material into which a patient specimen is placed for transport, storage, or testing.

Validated: Confirmed by examination and provision of objective evidence that the particular requirements can be consistently fulfilled.

FLOWCHARTS - ALL DEVICES EXCEPT INVITRO

NOTE: The first attached flowchart is shown in color and is for purposed of orientation only (page size was originally 19inx19in for printing and viewing). If all of the flowcharts were placed together, this is what the total flowchart would look like. The sections of the flowchart were placed individual pages and made black and white for ease of printing and viewing.

NOTE: Changes due to the passage of the Food and Drug Administration Modernization Act of 1997 are not reflected in the text or flowcharts of this document. Separate guidance is currently being developed for the 30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes. That guidance will be integrated into this guidance when it becomes final.



PMA MODIFICATIONS FLOW CHART

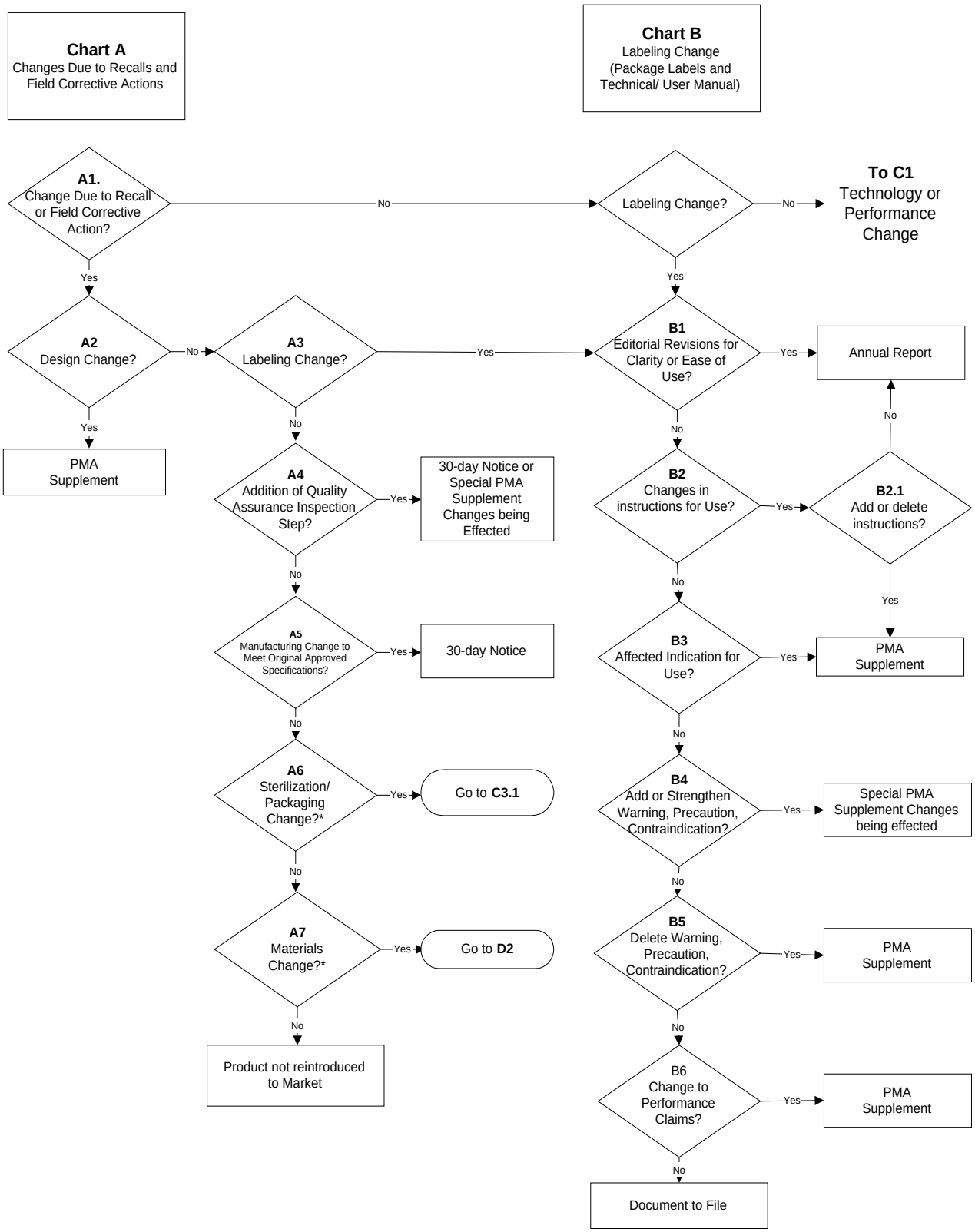


CHART C1
Technology or Performance Change

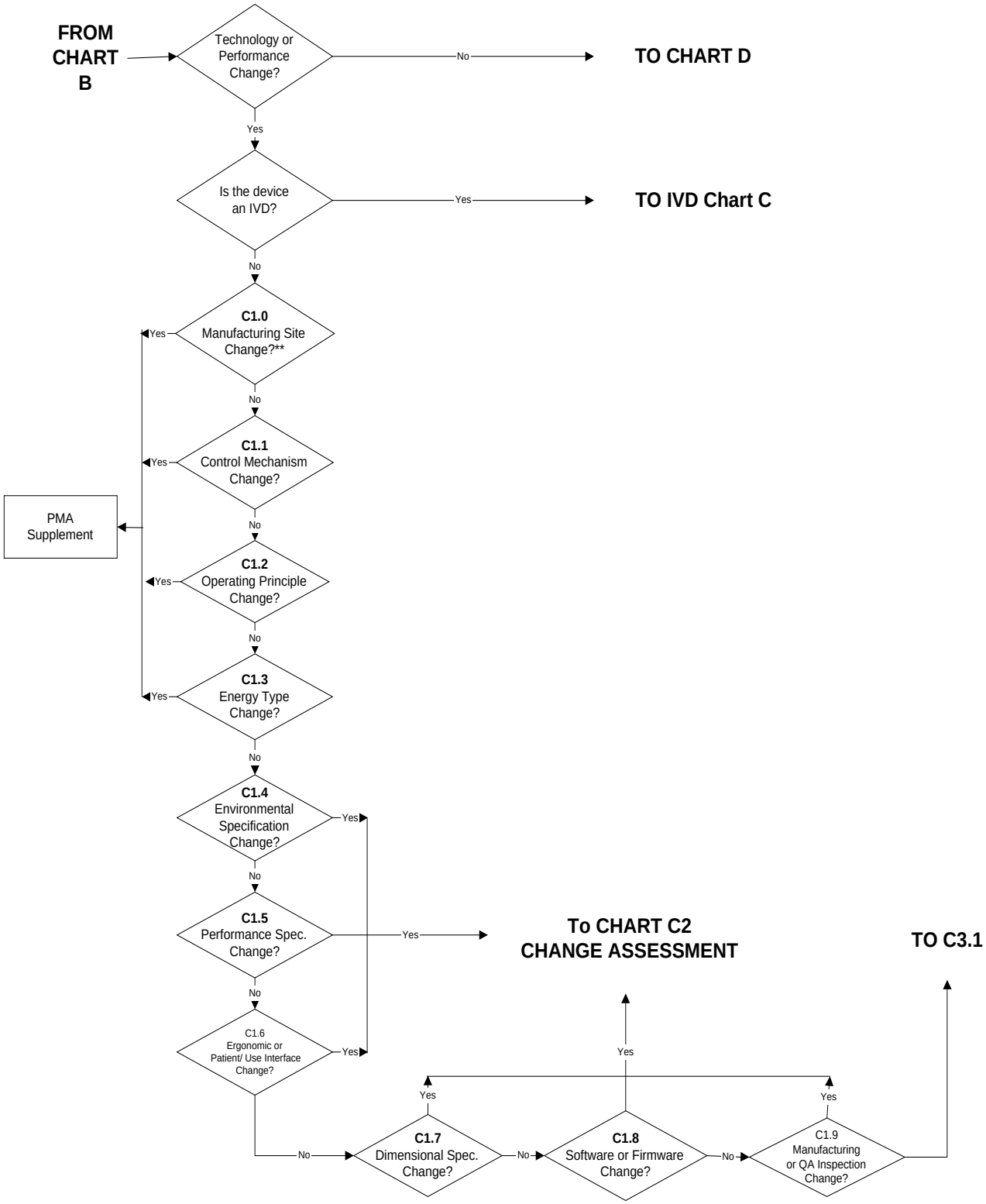


CHART C2
Change Assessment

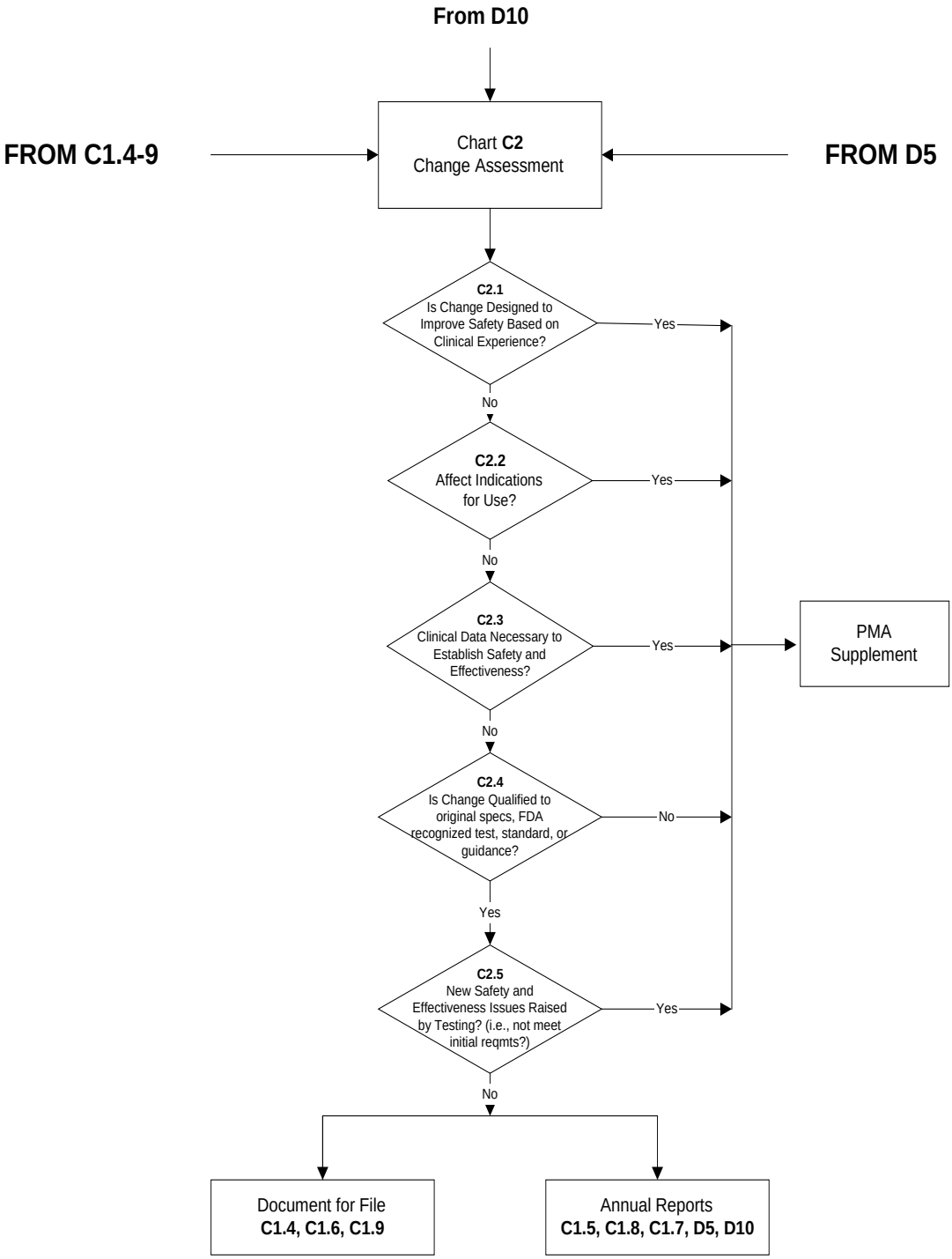


CHART C3
Packaging/ Sterilization Changes

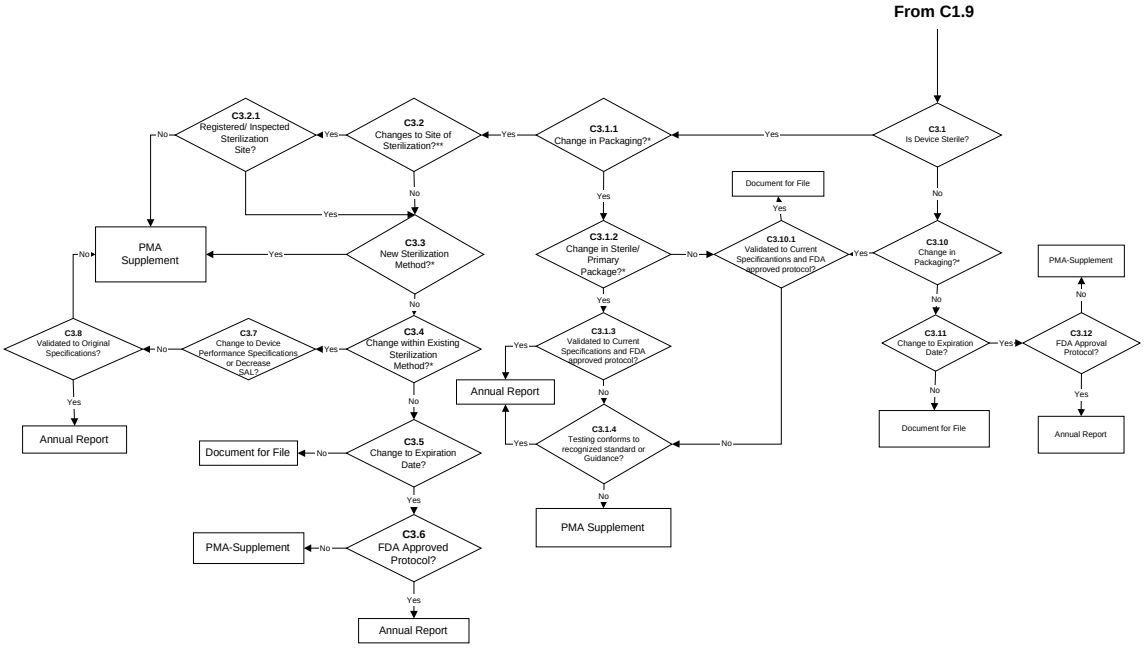
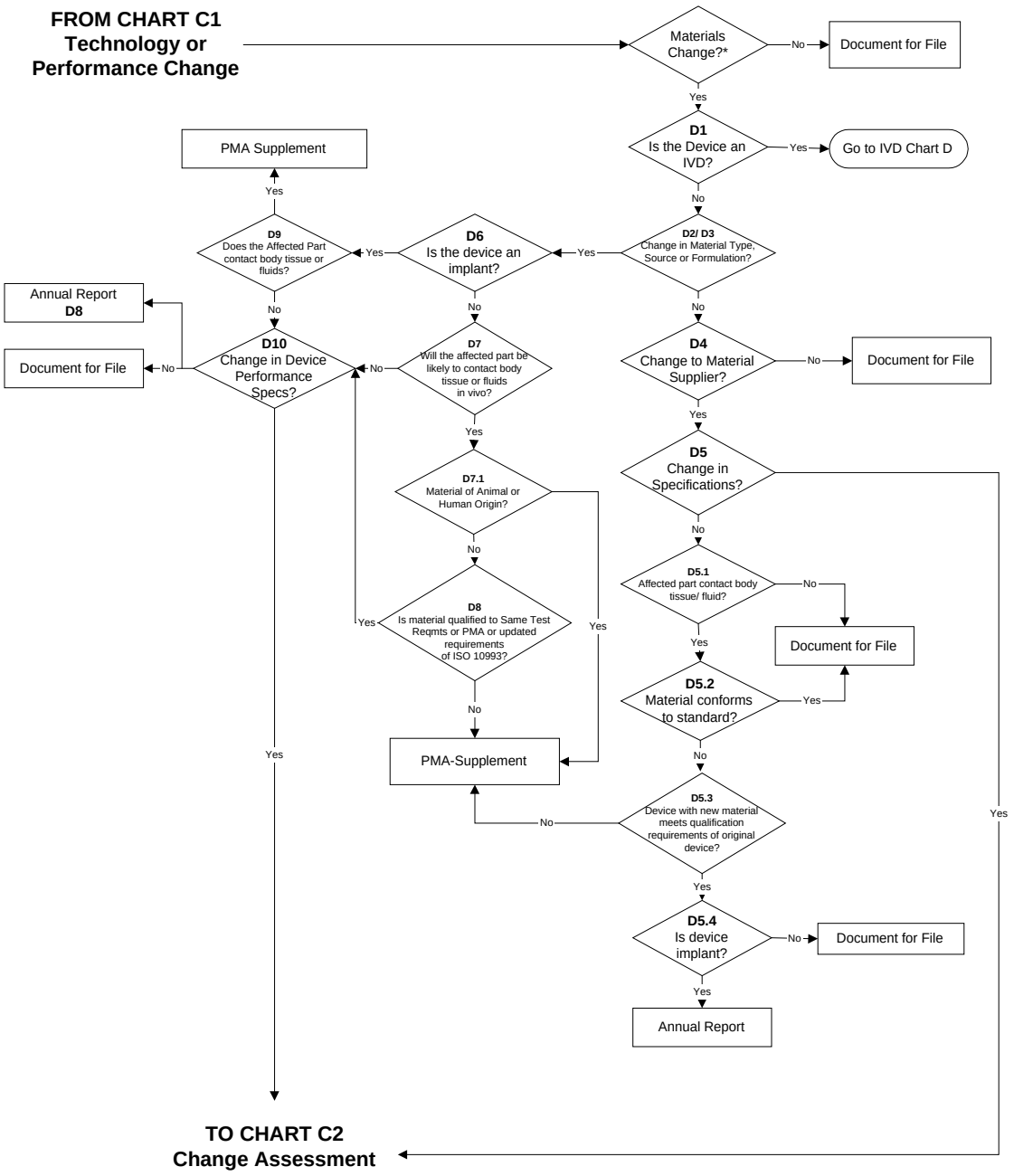


CHART D
Materials Change



FLOWCHARTS - IN VITRO DEVICES

Chart IVD-C_1
Technology or Performance Change

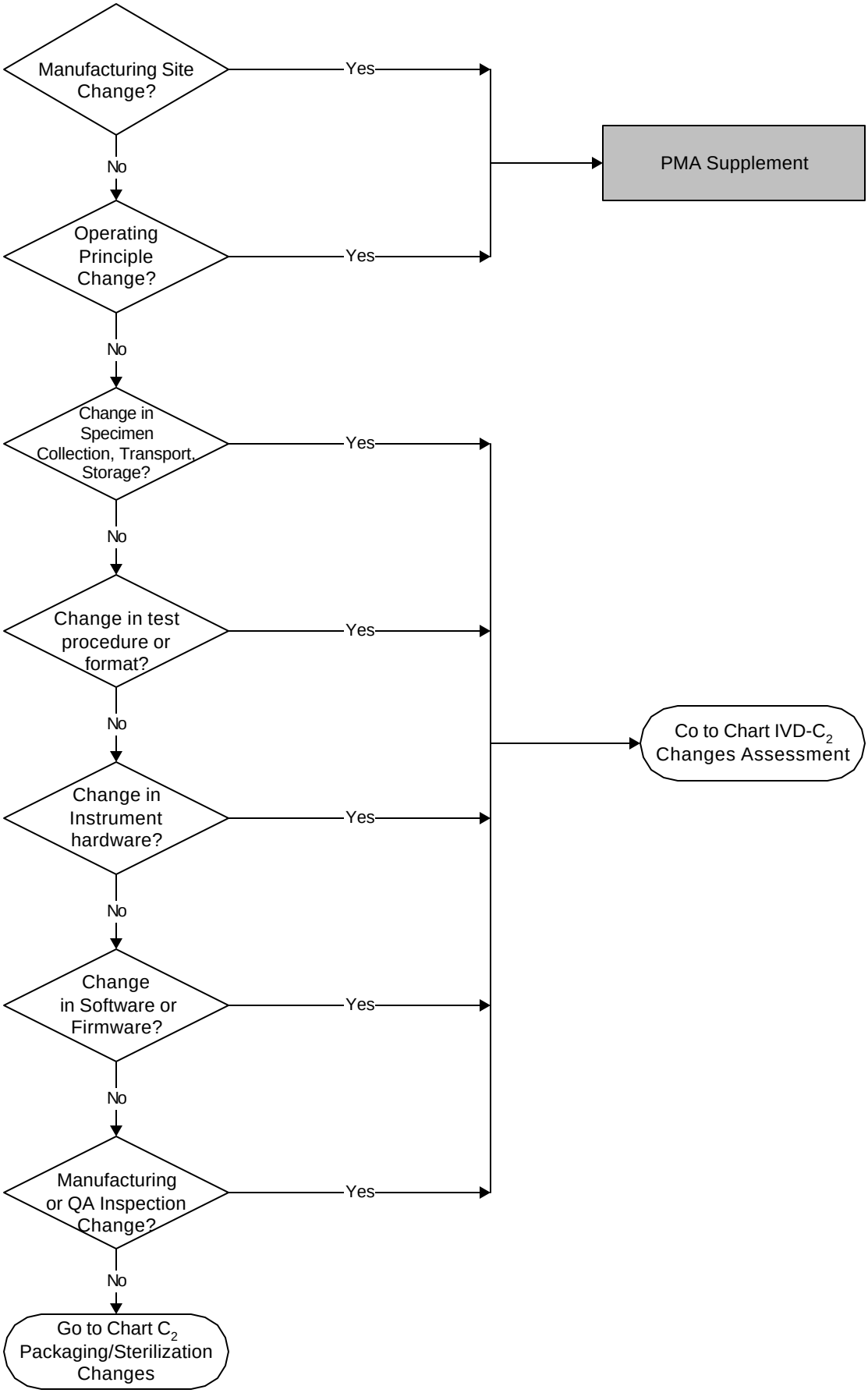


Chart IVD-C_2
Change Assessment

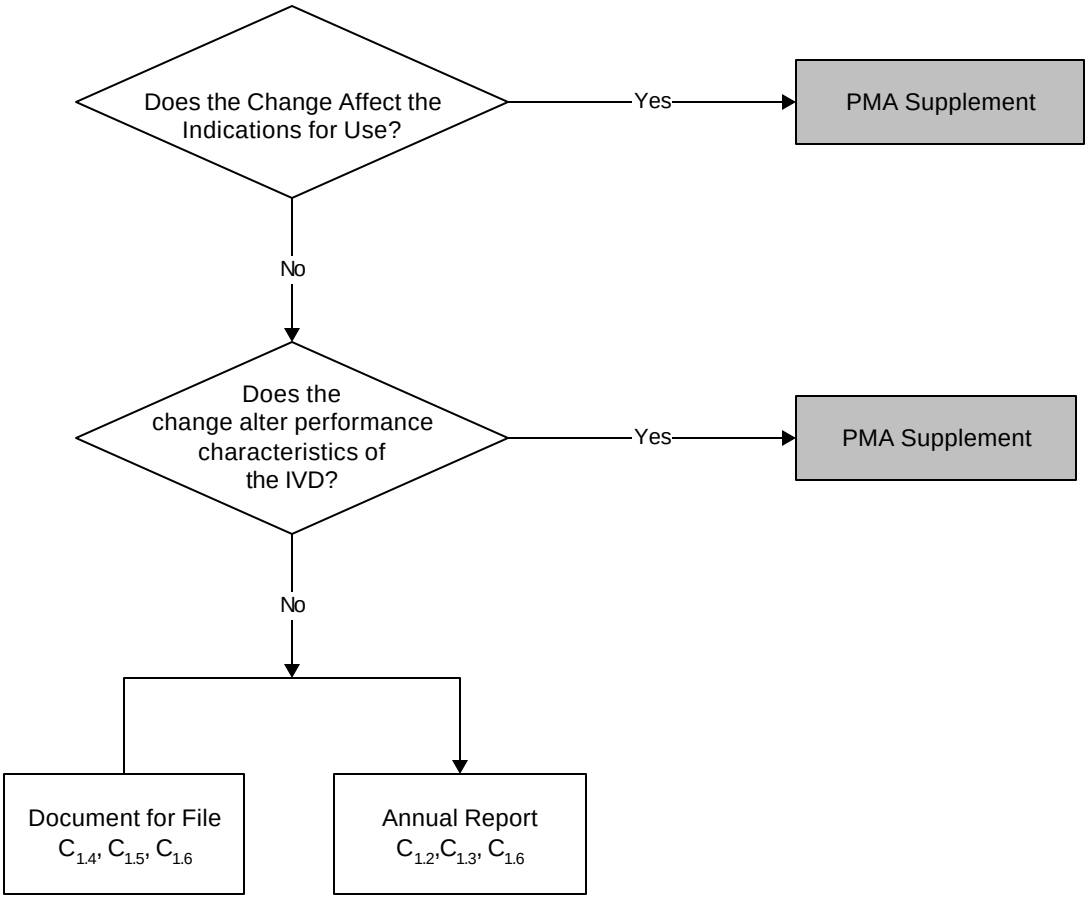


Chart IVD-D
Materials Change for IVD