Health Canada Santé Canada

January 20, 2011

Notice

Our file number: 11-100191-899

Subject: Guidance for the Interpretation of Significant Change of a Medical Device

Health Canada is pleased to announce the release of the *Guidance for the Interpretation of Significant Changes.*

The *Medical Devices Regulations* (*Regulations*) set out the requirements governing the sale, importation and advertisement of medical devices. The goal of the *Regulations* is to ensure that medical devices offered for sale in Canada are safe and effective and meet quality standards. Class II, III and IV medical devices sold in Canada are required to be licensed under section 26 of the *Regulations*. Section 34 of the *Regulations* describes five instances when a manufacturer is obliged to apply for an amended medical device licence. One of those instances is when a "significant change" is proposed to a Class III or IV device.

This guidance document elaborates upon the definition of "significant change" in the *Regulations*, in order to assist manufacturers in determining whether a change proposed to a class III or IV medical device requires the submission to Health Canada of a licence amendment application, prior to introducing the device to the market.

This guidance document will replace the *2003 Guidance for the Interpretation of Significant Change of a Medical Device*. The major changes include updated examples of significant changes and a restructuring of the guidance for additional clarity.

For further information on the revised *Guidance for Industry: Guidance for the Interpretation of Significant Change of a Medical Device*, please contact:

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GUIDANCE DOCUMENT

for the Interpretation of Significant Change

Published by authority of the
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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : *Ligne directrice sur l'interprétation d'une modification importante*

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy and quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1.0 INTRODUCTION

The purpose of this guidance document is to elaborate upon the definition of "significant change" found in the *Medical Devices Regulations 1998* (*Regulations*), in order to assist manufacturers in determining whether a change proposed to a class III or IV medical device requires the submission to Health Canada of a licence amendment application prior to the introduction of the device onto the market.

Medical devices are classified into one of four risk classes (I to IV) by means of classification rules set out in Schedule I of the *Regulations*, where Class I is the class representing the lowest risk and Class IV is the class representing the highest risk.

All Class II, III and IV medical devices sold or imported for sale in Canada are required to be licensed under Section 26 of the *Regulations*. Section 34 of the *Regulations* describes six instances when a manufacturer is obliged to apply for an amended medical device licence. One of those instances is when a "significant change" is proposed to a Class III or IV device.

The concept of significant change is linked to the principles of safety and effectiveness and the ability of a risk-based regulatory system to control the risk of medical devices offered for sale in Canada. Effective regulatory management of medical devices is based on a balance of pre-market review, post-market surveillance and quality systems. An accurate device licensing process is fundamental to all these processes.

Significant change is defined in the *Regulations*, and the definition is repeated in section 1.4 of this document.

The document provides a three-phased assessment tool that includes: general principles in identifying a significant change; a series of flow charts to aid in decision making; and a list of significant and non-significant change examples.

This guidance document replaces the previous 2003 guidance document, "Guidance for the Interpretation of Significant Change". This guidance document includes updated examples of significant change and has been reformatted into Good Guidance Practices (GGP) format.

1.1 Policy Objectives

To ensure that evidence of continued safety and effectiveness is submitted to Health Canada for a regulatory review and authorization when a significant change to a Class III and IV medical devices is proposed, and that modified medical devices for sale in Canada have an amended device licence.

1.2 Policy Statements

A manufacturer is required to submit a licence amendment to Health Canada for review and authorization once they have determined that the proposed change to a Class III or IV medical device is a significant change. Manufacturers may introduce the modified medical device, or components, for sale in Canada only upon receipt of an amended medical device licence from Health Canada.

However, a labelling change that adds a **contraindication, warning or precaution** vital to public health and safety should be implemented *immediately*, with a simultaneous licence amendment application being sent to Health Canada. A rationale explaining the need for the immediate change must be included in the licence amendment application, and is subject to final approval by Health Canada. The review time of these licence applications will be determined in consideration of both the nature of the changes involved and any potential patient safety concerns.

Manufacturers may submit to Health Canada a licence amendment fax-back form or licence amendment application for a change that is not identified as a "significant change" as referred to in Section 34 (b) through (f) under the *Medical Devices Regulations*, using the forms and guidance documents listed for reference in the Bibliography Section of this document.

All changes must be documented in the Quality Management System by the manufacturer. If changes have been found not to be significant by applying the principles of this guidance document and these changes are related to the information and/or documents originally submitted by the manufacturer with respect to the device licence application, then the changes must be reported to Health Canada at the time of annual licence renewal. These changes should be briefly itemized, in a tabular form with appropriate dates and with any necessary attachments.

1.3 Scope and Application

This Guidance document assists in the identification of "significant changes" to licensed Class III and Class IV medical devices. However, it does not specify the supporting safety and effectiveness evidence that should be submitted in the device licence amendment application.

A significant change is only one type of change that may require a manufacturer to obtain an amended medical device licence. When several simultaneous changes are being considered in the evolution of a licensed device, this guidance document should be used to assess each change separately, as well as the collective impact of the changes. A side-by-side comparison of the proposed changes to the currently licensed device may be useful. Changes normally eligible for notification by fax-back should not be included with the significant change amendment unless they affect the significant change.

In cases where the medical device is licensed as a system, test kit, group, family or group family pursuant to sections 28 to 31 of the *Regulations*, changes may be proposed to one or more of the component parts. This document should be used to assess each change separately, as well as the collective impact of the changes. Changes normally eligible for submission by fax-back should not be included with the significant change amendment unless they affect the significant change.

Manufacturers should also refer to other guidance documents, in particular the *Guidance for the Interpretation of Sections 28 to 31: Licence Application Type*, to determine how their proposed change(s) to a device may impact on the structure of a current licence. In some instances the applicant may be required to file for a new medical device licence rather than for a licence amendment application to a currently licensed device.

A modification to a device may involve changes to its design, functionality, manufacturing, packaging, finishing and labelling. A discussion of all possible changes is not feasible within the scope of this guidance document. If there are outstanding questions about a particular change, the manufacturer and/or device sponsor may contact Health Canada.

1.4 Definitions

Cautions and precautions are information which alerts the user to exercise special care necessary for the safe and effective use of the device.

Contraindications describe situations where the device should not be used because the risk of use clearly outweighs any reasonably foreseeable benefits.

Control mechanism is a means of verifying or checking that the specifications or outputs of the device meet a standard or predetermined result. They are mechanisms put in place to maintain on-going control or regulate the output of a device.

Facility means a site that is substantially involved in the manufacture or design and manufacture of a medical device.

Indications for use is the general description of the disease(s) or condition(s) the device will diagnose, treat, prevent or mitigate, including where applicable a description of the patient population for which the device is intended. The indications include all the labelled uses of the device, for example the condition(s) or disease(s) to be prevented, mitigated, treated or diagnosed, part of the body or type of tissue applied to or interacted with, frequency of use, physiological purpose and patient population. The indications for use are generally labelled as such, but may also be inferred from other parts of the labelling including the Directions for Use, Precautions, Warnings and bibliography sections.

Operating principles are the means by which a device produces or brings about an intended or appropriate effect. They are the means whereby a device is able to have a certain influence on a person or its surroundings.

Recall in respect of a medical device that has been sold, means any action taken by the manufacturer, importer or distributor of the device to recall or correct the device, or to notify its owners and users of its defectiveness or potential defectiveness, after becoming aware that the device:

(a) may be hazardous to health;
(b) may fail to conform to any claim made by the manufacturer or importer relating to its effectiveness, benefits, performance characteristics or safety; or,
(c) may not meet the requirements of the *Food and Drugs Act* or the *Medical Devices Regulations.*

Significant change means a change that could reasonably be expected to affect the safety or effectiveness of a medical device. It includes a change to any of the following:

(a) the manufacturing process, facility or equipment;
(b) the manufacturing quality control procedures, including the methods, tests or procedures used to control the quality, purity and sterility of the device or of the materials used in its manufacture;
(c) the design of the device, including its performance characteristics, principles of operation and specifications of materials, energy source, software or accessories; and
(d) the intended use of the device, including any new or extended use, any addition or deletion of a contra-indication for the device, and any change to the period used to establish its expiry date.

Surgically invasive device means an invasive device that is intended to enter the body through an artificially created opening that provides access to body structures and fluids.

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

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 Tools to Assess Changes

This guidance document presents three tools to assist manufacturers when assessing whether a change is considered to be a “significant change”:

1. The first tool is a generalized discussion of the broad principles that can be used to determine if a change would affect the safety and effectiveness of a medical device (section 2.2, “Significant Changes: General Principles”).

2. The nine flowcharts described in sections 2.3 to 2.11 (also presented in Appendices 1 - 9) are a second tool which details specific questions and answers to assist manufacturers in determining if a change is considered to be significant.

   Flowcharts A to H detail the most common types of changes made to medical devices. The "Main Flowchart" provides assistance in identifying which of these charts will be helpful. The accompanying discussions and flowcharts are intended to define the processes used to answer the question, "is this a significant change?". If the change is significant, then a licence amendment application must be submitted to Health Canada.

   Main Flowchart: General changes made to devices
   Flowchart A: Changes in manufacturing processes, facility or equipment
   Flowchart B: Changes in manufacturing quality control procedures
   Flowchart C: Changes in design
   Flowchart D: Changes to sterilization
   Flowchart E: Changes to software
   Flowchart F: Changes in materials for non *in vitro* diagnostic devices (IVDDs)
   Flowchart G: Changes in materials for IVDDs
   Flowchart H: Changes to labelling

3. The third tool (Appendix 10) is a list of examples of significant and non-significant changes. These examples are grouped according to the type of change.

Please note that the examples are not all-inclusive and may not apply in all cases.

2.2 Significant Changes: General Principles

A significant change (refer to definition of "significant change" in section 1.4) means a change that could reasonably be expected to affect the safety or effectiveness of a medical device. Typically:

- results in risks to the patient not previously identified;
- increases the probability of existing hazards occurring;
- alters the presentation of existing or new risks to the user (this can involve labelling changes or new indications for use); and/or,
- changes the performance, safety or effectiveness of the device.

For any change contemplated, a manufacturer must consider the device in question, the impact of the change on the patient, practitioner and/or user of the device, and the impact of the change on the specifications of the device, and decide whether the change could reasonably be expected to impact the safety and effectiveness of the device.

When considering several simultaneous changes, this guidance document should be used to assess each change separately, as well as the collective impact of the changes.

Health Canada does not generally consider the addition of new devices which are within the existing range of device sizes already licensed and are of the same design to be a significant change. These changes do require verification and validation to ensure that the safety and effectiveness of the device is not altered. However, if the addition to the existing range of device sizes is also accompanied by other design modifications, the change should be assessed to determine whether they constitute a significant change. For information on verification and validation and other contents of the application process, please see Health Canada's guidance, "*Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications, v.2*".

2.3 Main Flowchart

This flowchart describes the general types of changes that can be made to a medical device. It leads the manufacturer to more detailed information contained in Flowcharts A to H. If the determination is not straightforward, consult with the Medical Devices Bureau.

2.4 Flowchart A - Changes to Manufacturing Processes, Facility or Equipment

A change to the manufacturing process, facility or equipment that impacts the safety or effectiveness of a device is significant, and therefore an amendment is required. For example, this may include changes to the packaging process, which is a component of manufacturing.

In cases where the manufacturer's name and address on the device labelling stays the same but a new manufacturing facility is added, the new facility will need to be covered by the manufacturer's quality management system certification. The manufacturer is also required to submit a licence amendment faxback form for a change in manufacturer's name or address for Class III and IV devices. A template attestation letter, declaring the manufacturing specifications to be the same in the new manufacturing facility, has been added to this fax-back form. If the manufacturer makes this attestation, an amended licence may be issued without further evidence of safety and effectiveness.

When a supplier's manufacturing process, facility or equipment changes, this is not a significant change provided device specifications have not been changed and incoming inspections to evaluate the material/equipment provided by the supplier have not been changed.

Changes in sterilization procedures are often considered to be significant. Please refer to Section 2.7 on Sterilization and Flowchart D for clarification.

2.5 Flowchart B - Changes to the Manufacturing Quality Control Procedures

Changing or adding a new test acceptance criteria or test method to provide equivalent or better assurances of reliability is not considered to be a significant change. Removal of test acceptance criteria, in-process inspections, or final inspections without replacement of these activities is considered significant.

Changes to the manufacturing quality control procedures, such as the methods, tests or procedures used to control the quality, purity and sterility of the materials or the device, are considered significant if they alter the design specifications of the device. In these cases a licence amendment application is required, and the manufacturer is referred to Flowchart C for further guidance.

For example, changes to the manufacturer's requirements for material acceptance criteria can be considered a significant change if these changes alter the design specifications of the device.

2.6 Flowchart C - Changes in Design

Changes in design span the full spectrum from minor engineering changes to major changes in operating principles. All design changes must be evaluated, verified and validated according to the accepted procedures recorded in the quality management system. The results of this verification and validation process for each proposed change are then used to determine whether a licence amendment application is required.

2.6.1 Control Mechanism

Almost all changes in the control mechanism of a device raise questions of safety and efficacy. Therefore, in most circumstances, these changes require a licence amendment application.

2.6.2 Operating Principles

Similar to changes in the control mechanism, changes to the operating principles, including a change in the source of energy used by the device, usually require a licence amendment application. These changes are often accompanied by significant changes to device labelling.

2.6.3 Design Specifications

Changes to the design specifications, physical description, patient or user interface, software or firmware may be significant if they affect the indications for use of the device.

If the response to any of the following three questions is yes, then it is likely that the design change is significant and a licence amendment application would be required.

(1) Does the design change affect the indications for use?

(2) Are clinical data necessary to support the safety and effectiveness of the altered device?

(3) Do the results of a risk analysis, undertaken during the design verification and validation process, raise new issues of safety and effectiveness.

In cases where the change consists only of tightening of design specifications within specified tolerances and where there is no creation of new features, the change is not considered to be significant.

2.7 Flowchart D - Changes to Sterilization

The nature of sterilization is such that it is impossible to determine by inspection and testing if the sterilization of the actual device(s) has been successful. Medical devices are considered sterile if manufacturers can demonstrate a sterility assurance level (SAL) of 10^{-6} or better. The sterilization process needs to be verified and validated and its performance routinely monitored. For this reason, the Medical Device Bureau requires documentation pertaining to changes in sterilization method or process for medical devices or to any changes that might affect the effectiveness of the process.

Such changes include:

- Changes that increase the bioburden alert or action levels or that introduces an organism that is more difficult to kill
- device design and material changes that introduce a feature that is more difficult to sterilize;
- changes in sterilization process or equipment or cycle parameters;
- changes in the density or configuration of the sterilization load;
- changes to the quality control verification and validation process such as introducing parametric release.

This rationale also applies to changes in the packaging of medical devices subject to sterilization. In general, any change to the sterilization method or process of a medical device, or a change to the packaging for the sterilization of a medical device is considered to be a significant change. Changes in packaging characteristics of a sterile medical device, configuration or density could affect the absorption or penetration of the sterilant, the residue levels (where applicable) and the effectiveness of the sterilization process in addition to the safety of the sterile device. Issues of compatibility between the packaging material and the sterilization process must also be taken into consideration to ensure that seal integrity is not affected and that the packaging preserves the functionality and safety of the device throughout its declared shelf-life.

However, if a change to the packaging of a sterile medical device or a change in the sterilization method or process has been reviewed in a previous application for similar devices, the change can be considered a non-significant change for the current application, as long as the proposed device is not more difficult to sterilize than the previously licensed device. This classification as a non-significant change only applies to devices of identical material and similar design and only if the proposed changes have been wholly and completely represented and approved in a previous application.

Adding a new test acceptance criteria or test method, over and above the existing process, to provide equivalent or better assurance of sterility, reliability or similar safety aspects is considered to be a non-significant change. However, if a proposed change is made from a non parametric release to a parametric release, this is considered to be a significant change.

2.8 Flowchart E - Changes to Software

Many changes to a device's software will require a licence amendment application.

The following would be considered significant changes:

- a software change, which impacts the control of the device, that may alter the diagnosis or therapy delivered to the patient;
- an alteration in software that modifies an algorithm impacting the diagnosis or therapy delivered;
- a software change that impacts the way data is read or interpreted by the user, such that the treatment or diagnosis of the patient may be altered when compared to the previous version of the software;
- a software change that replaces previously required user input a closed loop decision;
- addition of a new feature to the software that may change the diagnosis or therapy delivered to the patient;
- introduction to or removal of a new alarm function from the software such that a response to the new configuration may change the treatment of the patient in comparison to the previous version of the software;
- a software change that incorporates a change to the operating system on which the software runs.

If the software is modified to correct an error (for example, a change in algorithm), for which there is a safety risk to the patient if the error is not corrected, this software change may require a licence amendment application. In such instances and where the software change is a corrective or preventative action for a recall, consultation with the Medical Devices Bureau is recommended to determine if the change requires a licence amendment application.

If a software change is only intended to correct an inadvertent logic error that does not pose a safety risk and brings the system back into specification, this is not a significant change.

The following would **not** be considered significant changes:

- a software change that only introduces non-therapeutic and/or non-diagnostic features such as printing, faxing, improved image clarity, reporting format or additional language support;
- a software change that only modifies the appearance of the user interface with negligible risk of impacting the diagnosis or therapy delivered to the patient;
- a software change that disables a feature that does not interact with other features.

2.9 Flowchart F - Changes in Materials for non *in vitro* diagnostic devices (IVDDs)

Changes to the materials of a non *in vitro* diagnostic device (IVDD) may lead to subsequent changes, such as manufacturing processes, equipment, labelling or changes to the device performance specifications, and these must also be considered separately. The following changes should be considered before applying the logic scheme presented in Flowchart F for material changes:

(1) All changes to the sourcing or processing of materials of human or animal origin are considered significant and result in a licence amendment application.

(2) Changes within a single generic material type or changes in formulation can affect the chemistry, metallurgy or other property, such as stability, of the device.

In each of the above instances, it must be determined if the device is a surgically invasive device intended to be absorbed by the body or to remain in the body for at least thirty consecutive days. If this is the case, and the altered material would be in contact with body tissues or fluids, then a licence amendment application is required. Even when the material would not be in contact with body tissues and fluids, the question of design specifications arises. If changes to the design specifications are required, they should be reviewed with the guidance of Flowchart C.

In cases where devices are not intended to be absorbed by the body or to remain in the body for at least 30 consecutive days, but where the altered material is in contact with body tissues or fluids a licence amendment application is required unless the new material meets the existing specifications. As in other cases, changes to performance specifications must be considered with the aid of Flowchart C.

If the supplier or vendor of the material changes, but the material meets the manufacturer's previously reviewed acceptance criteria, with the exception of human or animal derived materials, then that change is not significant.

2.10 Flowchart G - Changes in Materials in *in vitro* diagnostic devices (IVDDs)

There is a distinction between IVDDs and other devices with regard to material changes. This section also considers changes to the method used to perform a licensed test.

Changes to materials in an IVDD often affect its performance characteristics, including specificity or sensitivity, and would be assessed as to their impact on the safety and effectiveness of the device.

Changes to materials that necessitate the testing of additional clinical samples to determine the performance characteristics of the IVDD would be considered a significant change, unless the additional clinical testing only confirms that the altered IVDD still conforms to the licensed performance specifications and no labelling changes are necessary.

Changes to the materials of an IVDD that result in a change to the operating principle of the product (for example, change from Immunofluorescence to ELISA) are considered significant and require the submission of a licence amendment application.

Changes to materials that potentially affect the operating principle of an IVDD include changes in reaction components or materials such as calibration materials, or changes in methods such as specimen pretreatment, incubation times and temperatures. If these changes result in altered performance characteristics that are reflected in the labelling, then a licence amendment application is required.

2.11 Flowchart H - Changes to Labelling

Changes to a device, including changes to performance specifications and materials, often lead to labelling changes. Labelling changes also occur in response to changing user requirements. Each labelling change must be considered separately and the manufacturer should refer to the logic scheme presented in Flowchart H.

Changes to the intended use or indications for use will require a licence amendment application unless the changes are within an approved set of indications. Changes within an approved set of indications should be submitted at annual renewal or as an immediate file update. However, if a limitation to the indications for use is introduced as a result of concerns associated wit the safe and effective use of the device, a contraindication must be added. This is considered a significant change.

Minor changes to clarify the existing wording of the warnings and precautions for a device may not trigger the need for an amended licence application. However, in the case where these changes add or remove a contraindication, or remove a warning or precaution, an amended licence application is required.

The deletion of a contraindication, such as “not for pediatric use” is considered a significant change and requires a licence amendment application.

Changes made to device labelling solely for the purposes of clarifying instructions in order to make the device easier, safer or more effective to use will not require a licence amendment application. For example, device labelling often requires modifications in language and structure to be used by a lay person. Provided no changes are made in the indications for use, these changes are not significant.

Changes to labelling to include additional languages required in other regulatory jurisdictions are not significant.

A change in the shelf life for *in vitro* diagnostic devices is considered a significant change.

Generally, a change in the shelf life of a non IVDD will not require a licence amendment. However, if the protocols and methods for determining shelf life have been changed or have not been reviewed in a previous licence application, a licence amendment is required.

3.0 PROCESS AND PROCEDURES

3.1 Significant Changes - Licence Amendment Application

A licence amendment application must be made using the "Application for Licence Amendment" form for a Class III or IV device with a significant change. This application will be processed in accordance with the *Management of Applications for Medical Device Licences and Investigational Testing Authorizations Policy*.

In addition to the application form, a premarket review document applicable to the risk classification of the device must be submitted. Identical changes made to Class III and IV devices may result in different review components being submitted. The review components submitted must contain information and documents that are relevant to the change (Refer to the guidance document, *Preparation of a Premarket Review Document for Class III and IV Device Licence Applications GD008*).

3.2 Recall

Changes occurring as a result of a recall are to be assessed to determine if they are significant, including design changes or design specification changes required to bring a medical device back in line with previous performance specifications. Cover letters accompanying device licence amendment applications in response to a recall should clearly identify that the amendment application is being submitted for this purpose. Please contact the Medical Devices Bureau to further follow-up on applications of this nature. Following a recall, the review time of these licence applications will be determined in consideration of both the nature of the changes involved and any potential safety concerns.

4.0 BIBLIOGRAPHY

Guidance for the Labelling of Medical Devices under Section 21 to 23 of the Medical Devices *Regulations*, June 12, 2004.

Medical Devices Regulations (SOR/98-282), May 7, 1998.

Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications V.2, October 23, 1998.

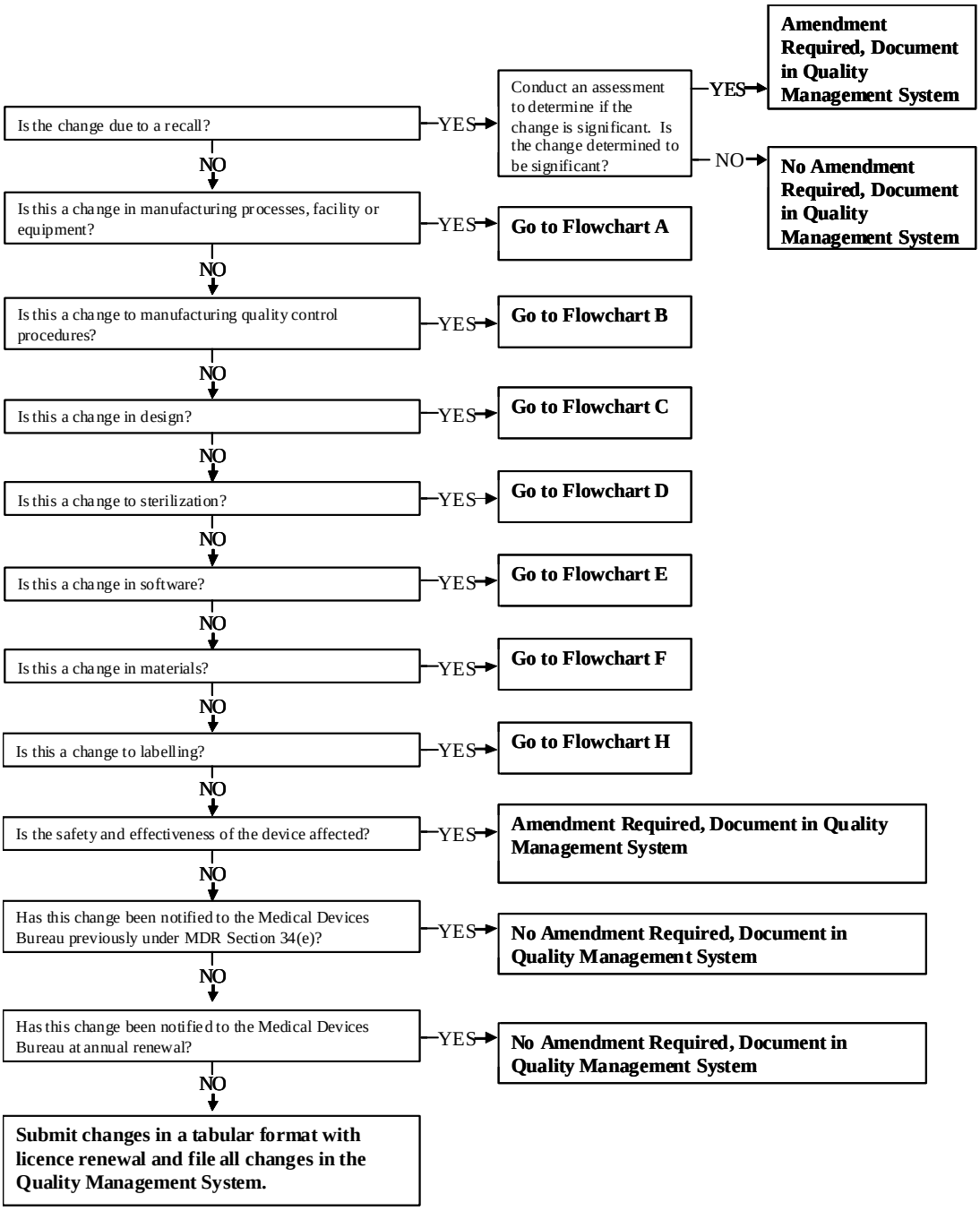
Medical Devices Licence Amendment Fax-Back Form - Guidance for Non-Significant Additions/Deletions (non-significant changes to catalogue numbers).

Medical Devices Licence Amendment Fax-Back Form - Guidance for Changes to Manufacturer's Name and/or Address of Existing Device Licences.

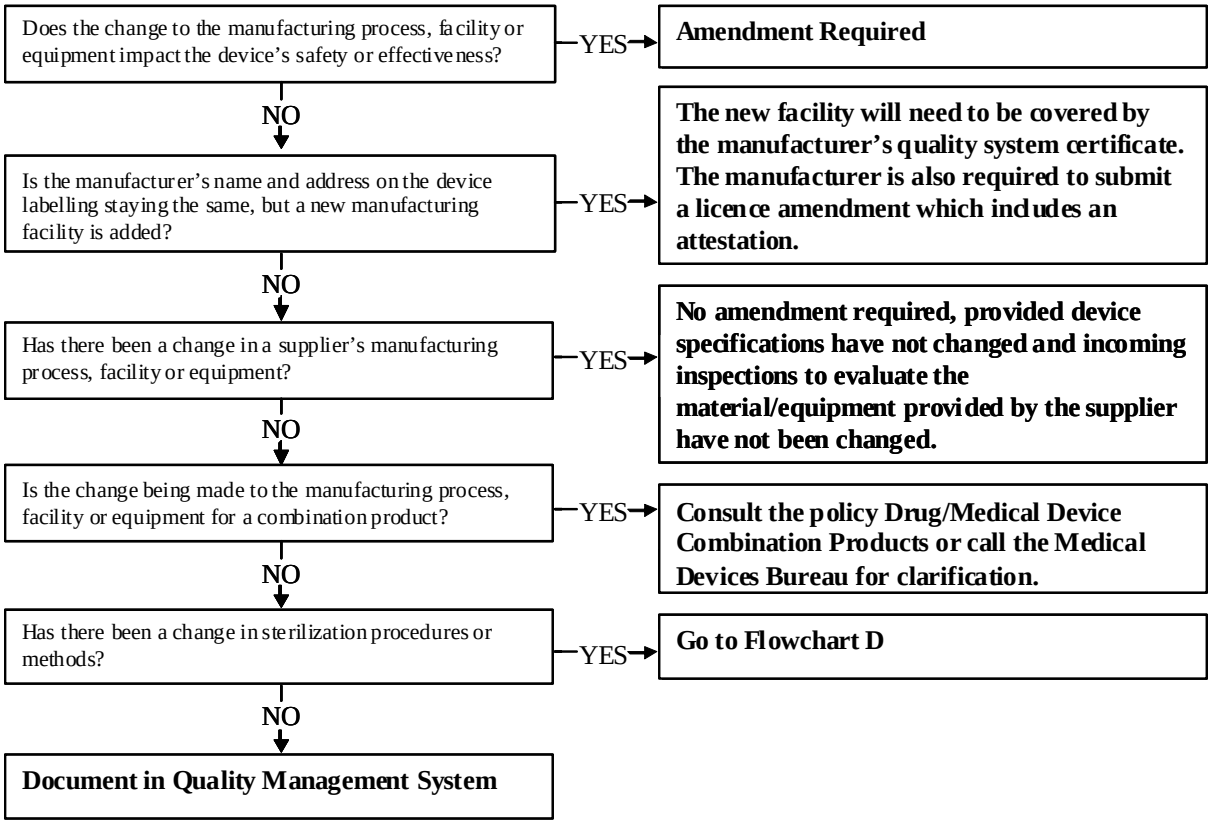
Licence Amendment Fax-Back Form - Guidance for Changes to the Name of a Device for Existing Device Licences.

Application for a Medical Device Licence Amendment.

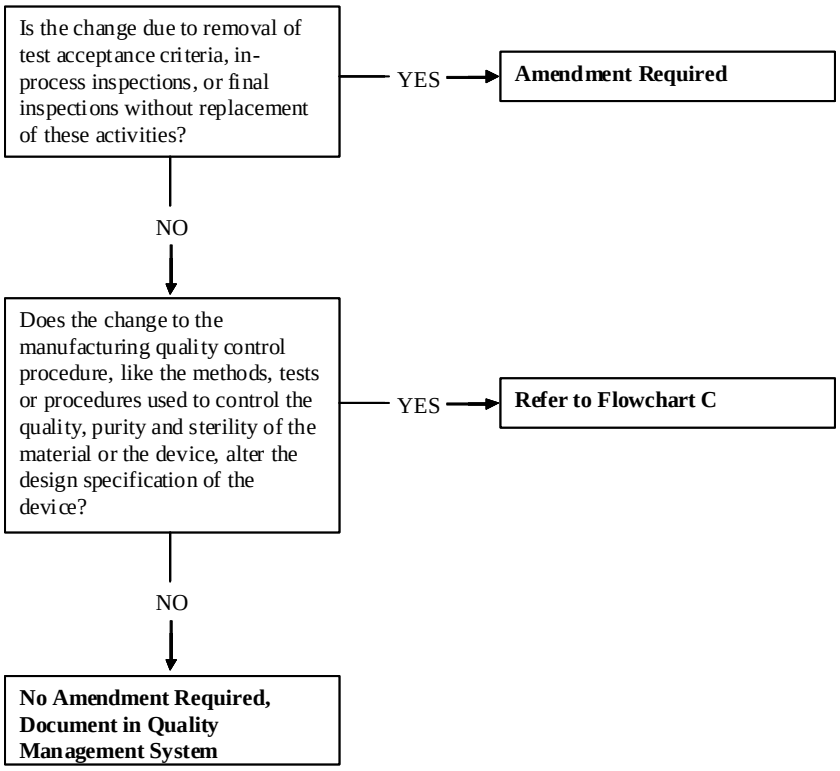
Appendix 1: Main Flowchart



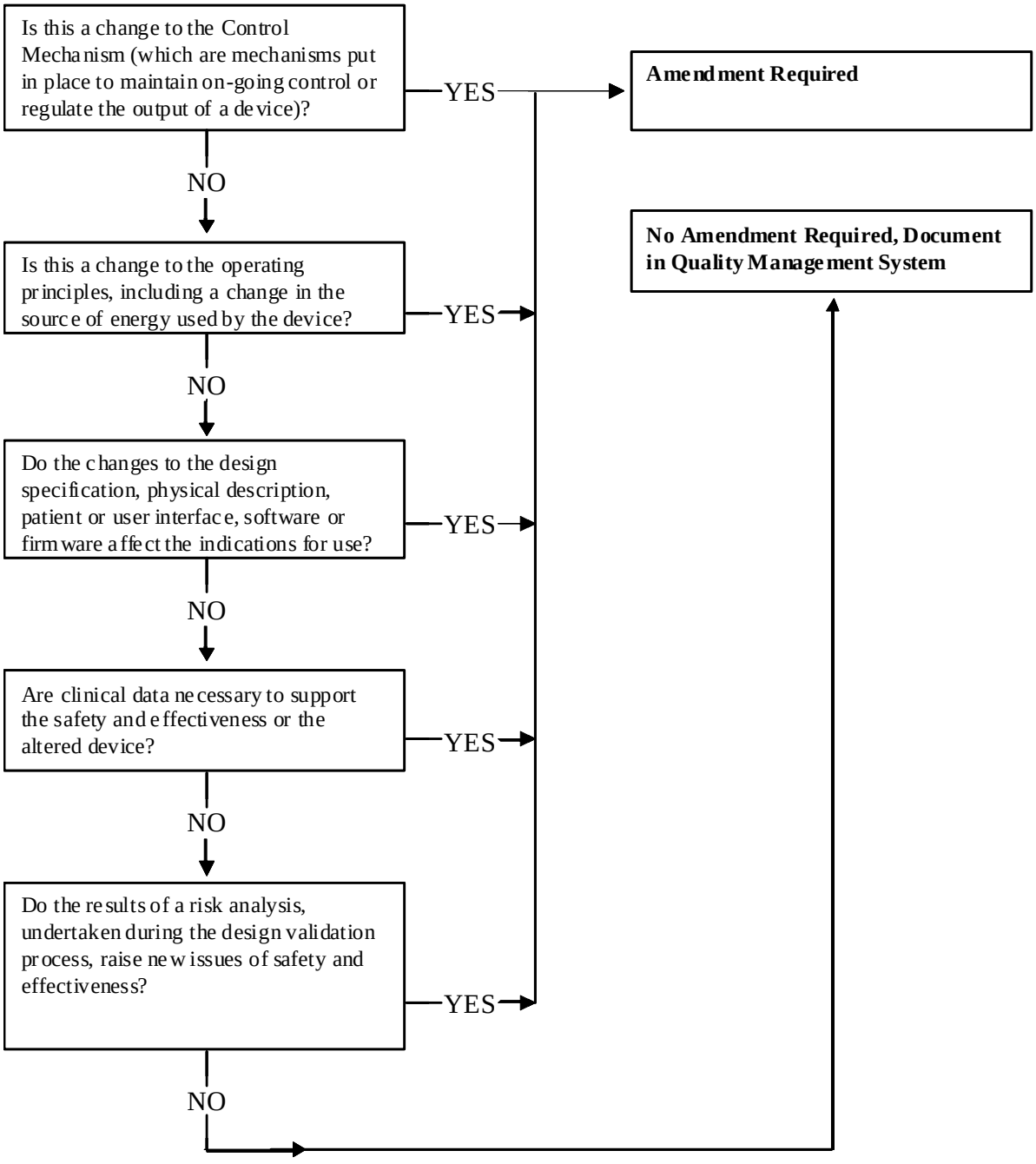
Appendix 2 - Flowchart A: Changes to Manufacturing Process, Facility or Equipment



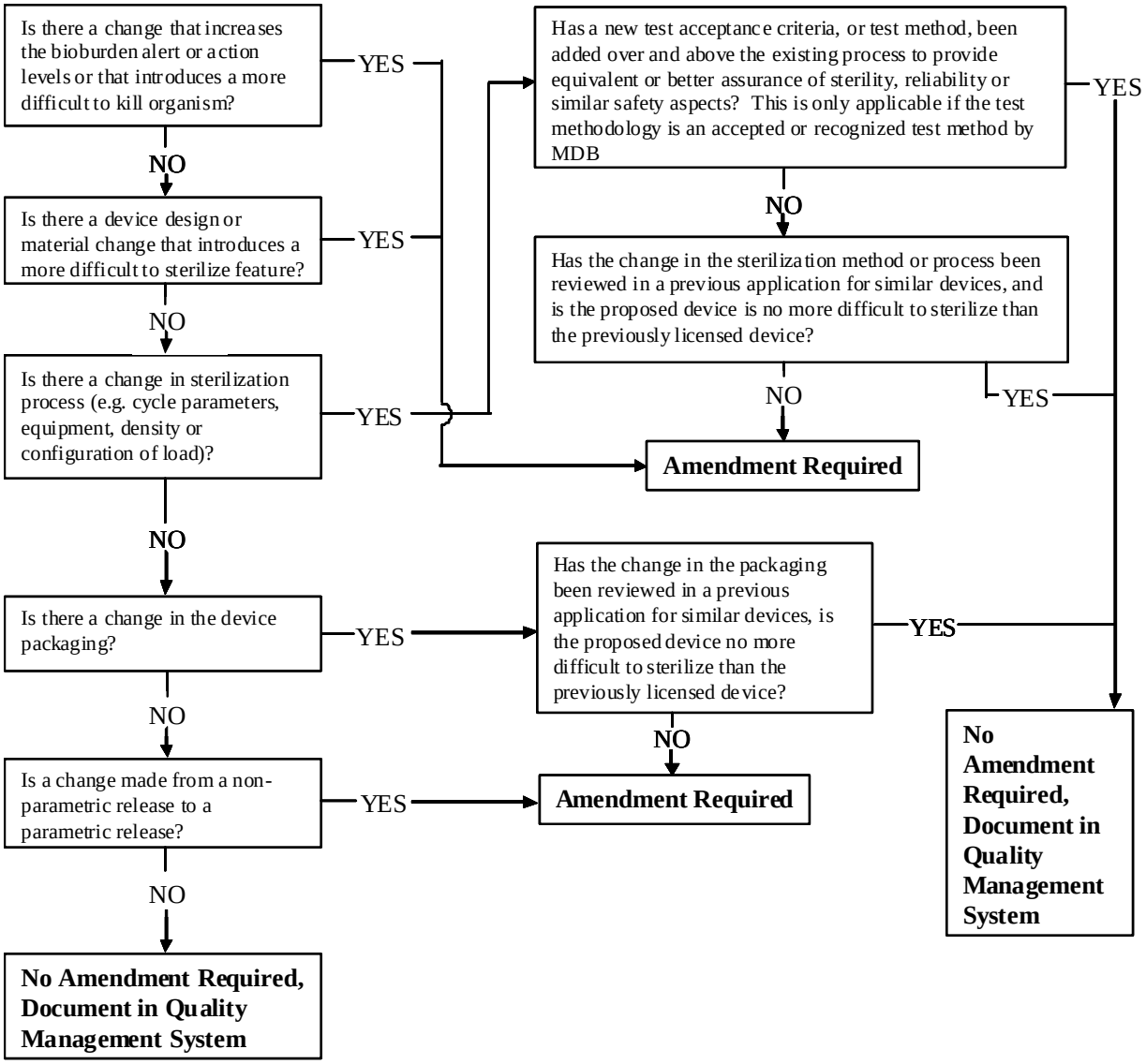
Appendix 3 - Flowchart B: Changes in Manufacturing Control Procedures



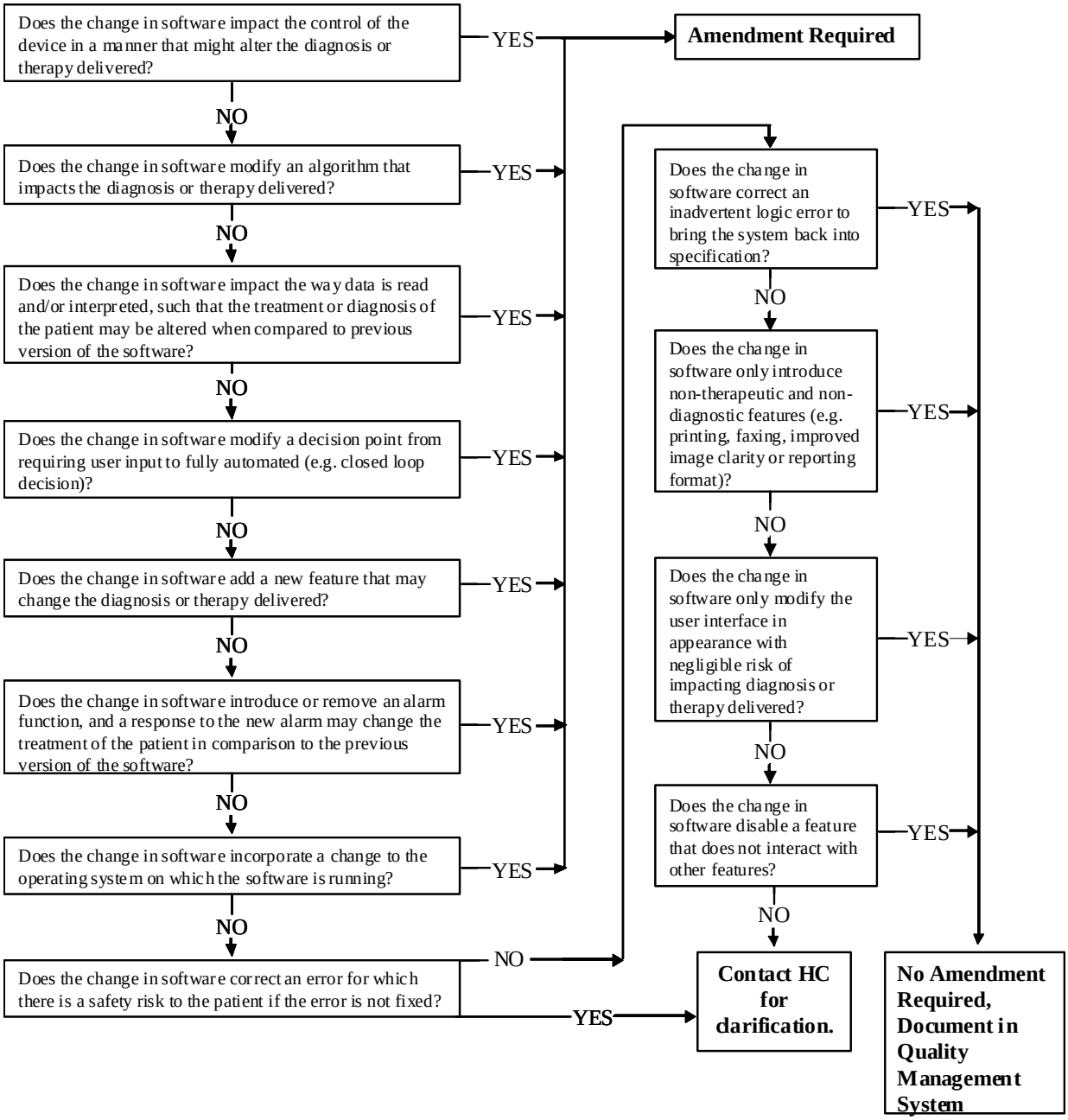
Appendix 4 - Flowchart C: Changes in Design



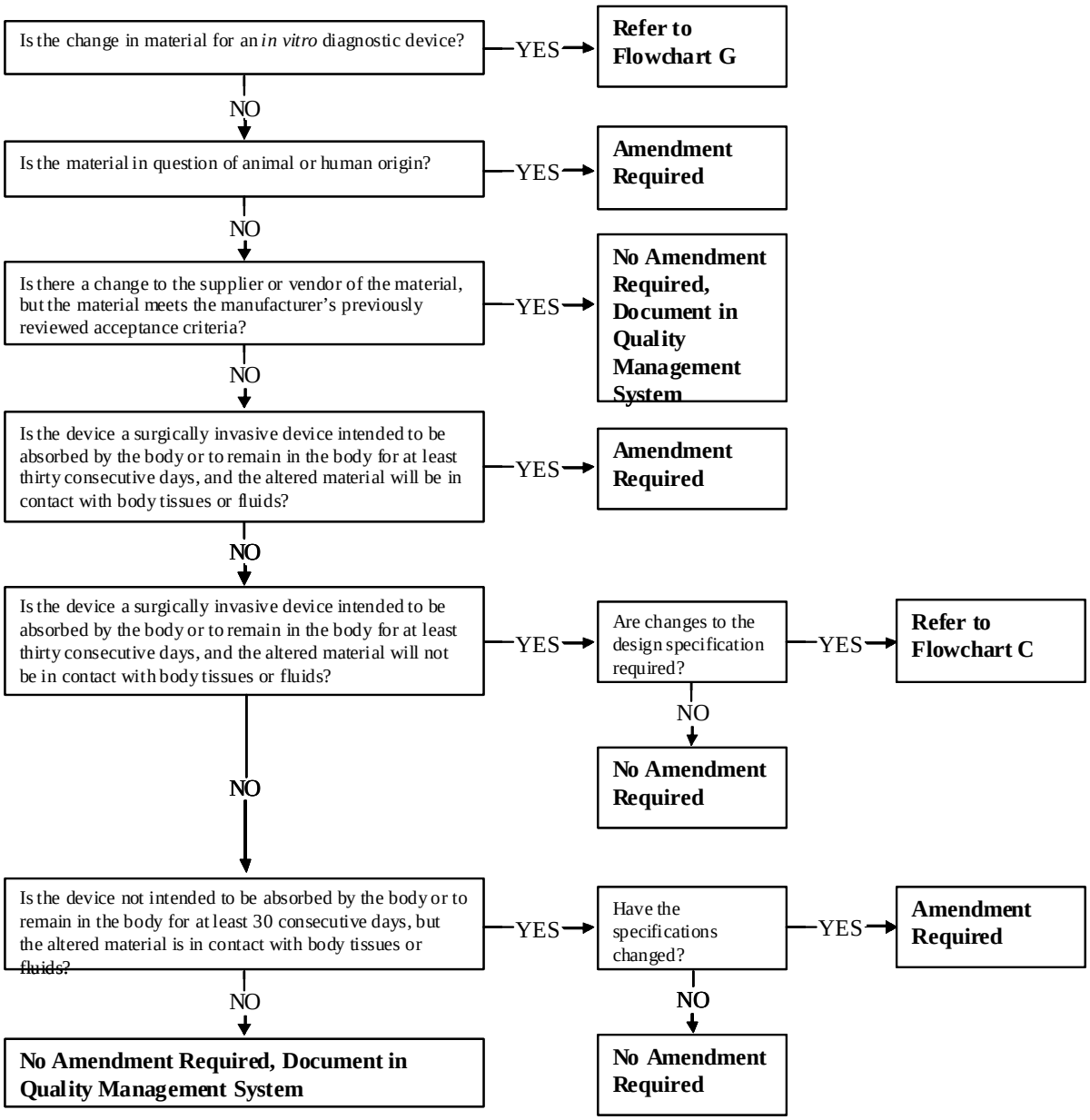
Appendix 5 - Flowchart D: Sterilization of Medical Devices



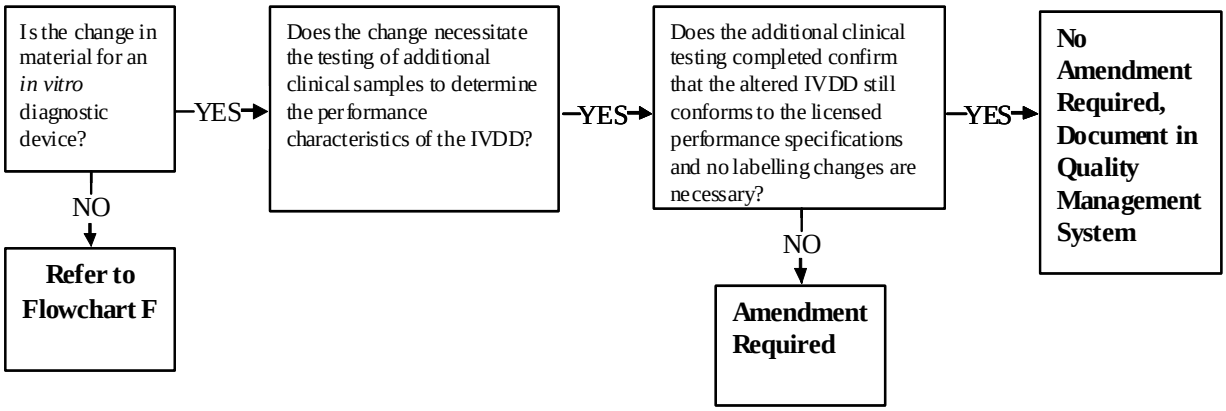
Appendix 6 - Flowchart E: Changes to Software



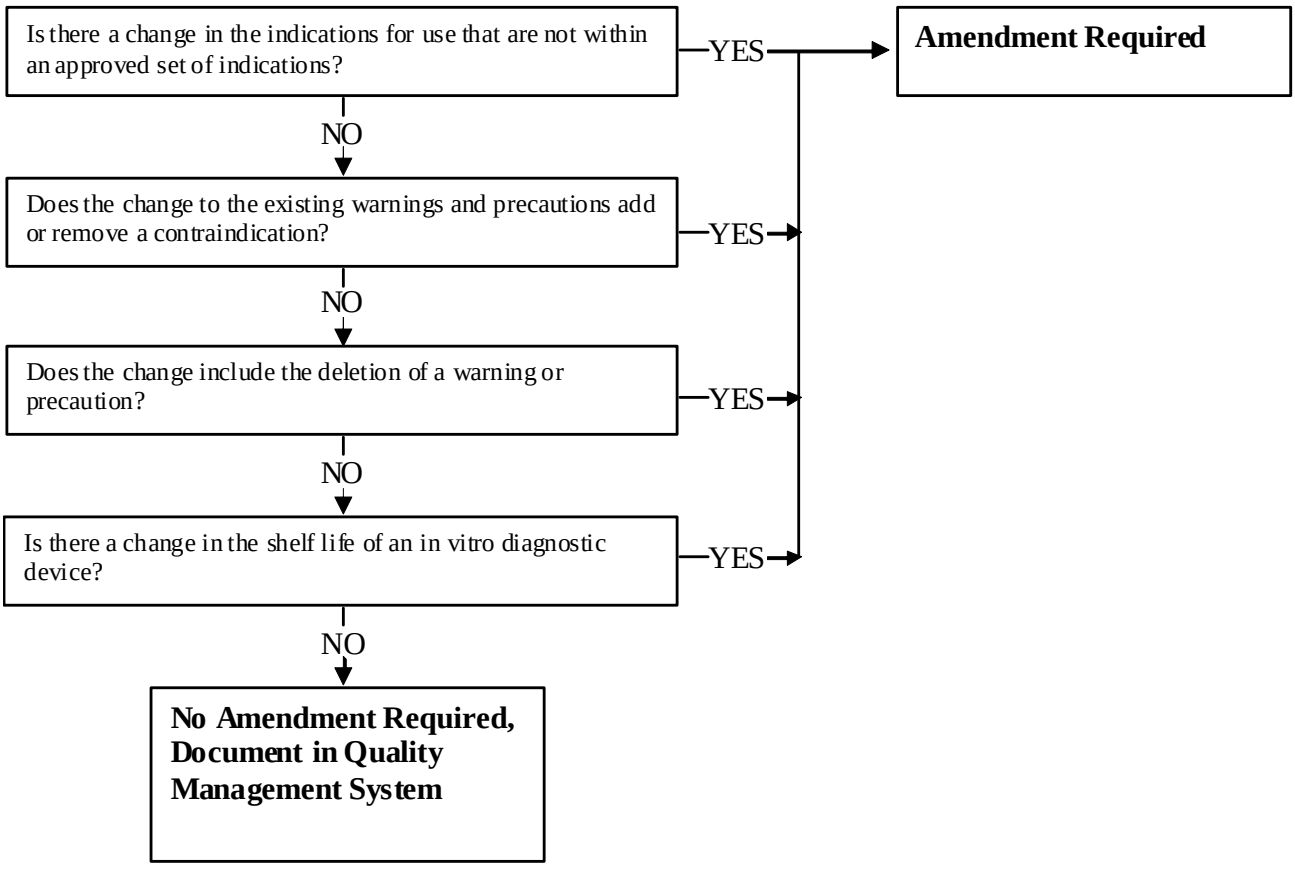
Appendix 7 - Flowchart F: Changes in Materials for non-IVDDs



Appendix 8 - Flowchart G: Changes in Materials for IVDDs



Appendix 9 - Flowchart H: Changes to Labelling



Appendix 10 - Table of Examples

Device	Proposed Change	Significant or Not
Changes to Manufacturing Processes, Facility or Equipment		
Non-sterile Devices	**A change in packaging from one variant of polyethylene to another due to supplier rationalization or cost saving measures. Validation and stability testing shows integrity has not been compromised.**	**No, this is not a significant change.**
Implantable Vascular Device made of Nitinol Mesh	**Modification of the manufacturing process of the device to change the way the nitinol fibres are weaved together. The new device is made of exactly the same material, but is denser.**	**Yes, this is a significant change.**
Drug Eluting Stent	**A manufacturing site change where a polymer and drug coating is applied.**	**Yes, this is a significant change.**
Catheters	**A change in supplier that extrudes the polymer tubing with no change in finished product performance specifications.**	**No, this is not a significant change.**
Changes in Design		
All Devices	**A change from an internal direct current (DC) power source to an external alternating current (AC) source or visa versa.**	**Yes, this is a significant change.**
All Devices	**The addition of a new foot switch (where there was not one before) to an electrosurgical generator or other device, addition of "hot keys" and corresponding software to the operating**	**Yes, these are significant changes.**

	console.	
Non-active Surgically Invasive Devices	**A change in the design characteristics that allows for additional or broader indications for use. For example, a smaller sized hip prosthesis or fracture fixation screw that are significantly different from their predicate designs.**	**Yes, these are significant changes.**
Catheters	**A change to the cable design and grip of a steerable ablation catheter, which results in improved deliverability and improved procedural times.**	**Yes, this is a significant change.**
Catheters	**A change to the grip of a steerable ablation catheter to provide improved ergonomic comfort for the healthcare professional or aesthetic presentation of the device without changing the functionality.**	**No, this is not a significant change.**
Endocardial Lead	**Additional polymer support clip added; intended to prevent the dislodging of the electrical connection and to increase the axial retention forces.**	**Yes, this is a significant change.**
Ultrasound Transducer	**An update in design of the grip portionto improve user comfort. This change does not affect the safety or performance of the transducer.**	**No, this is not a significant change.**
Hemofiltration System, including software controls.	**The addition of a new component, a combined filter and disposable cartridge for convenience.**	**Yes, this is a significant change.**
Transurethral Thermal System for the treatment of	**A change to the software, to provide automatic control of ramping power, respond to**	**Yes, this is a significant change.**

benign prostatic hyperplasia.	**elevated rectal temperatures automatically and adjust power.**	
Metallic Biliary Stent for treating malignant strictures.	**Addition of two new stent lengths.**	**Yes, this is a significant change, if the new stent lengths are outside of the range of the previously licensed stent lengths.**
Metallic Biliary Stent for treating malignant strictures.	**Addition of two new stent lengths.**	**If the new stent lengths are intermediate between the previously licensed stent lengths, this change is not significant.**
Total Knee System	**Addition of longer femoral augments.**	**Yes, this is a significant change.**
Total Hip System	**Addition of a new bearing surface.**	**Yes, this is a significant change.**
Acetabular Cups	**A change in design to offer additional flexibility to implanting surgeons. Additional holes are added to the cups.**	**Yes, this is a significant change.**
Bone Void Fillers and Putty	**A change to increase in the amount of cancellous bone material in the filler.**	**Yes, this is a significant change.**
Anaesthesia Machine	**A change in the sensor controlling the fresh air proportions.**	**Yes, this is a significant change.**
Automatic Implanted Cardiac Defibrillator	**Alteration of the internal components, including the capacitors, telemetry coils, batteries and transformers with the aim of improving efficiencies in the device operations.**	**Yes, this is a significant change.**
Cardiac Pacing Leads	**The addition of two or more electrodes, or a new anchoring mechanism can result in new indications for**	**Yes, these changes are significant.**

	use, as well as enhanced performance claims.	
Pacing Lead	**Reduction in size of the wire diameter to reduce the overall lead diameter, facilitating smaller introduction into the vessel.**	**Yes, this is a significant change.**
Left Ventricular Pacing Lead	**Modification of a detachable handle that allows the user to torque the lead body in order to provide a more ergonomic feel.**	**No, this is not a significant change.**
Patent Foramen Ovale (PFO) Closure Device	**Addition of an 18 millimetre (mm) PFO closure device to a licence that includes a 16 mm PFO closure device and a 20 mm PFO closure device. The basic design and delivery system are the same.**	**No, this is not a significant change, as the new closure device is within the range of existing sizes.**
***In Vitro* Diagnostic Devices (IVDD) Test Kit**	**A change in sample matrix for an IVDD test kit from a venous blood sample to a dried blood spot.**	**Yes, this is a significant change.**
Clinical Chemical Analyzer	**A change to the throughput**	**Yes, this is a significant change.**
Clinical Chemical Analyzer	**A change to the test volume.**	**Yes, this is a significant change.**
Clinical Chemical Analyzer	**A change to the full automation.**	**Yes, this is a significant change.**
Blood Glucose Monitor	**Addition of a new control**	**Yes, this is a significant change.**
Blood Glucose Monitor	**Reduction in the sample volume made by a change to the electrode layout which reduces the test strip sample chamber volume.**	**Yes, this is a significant change.**
Blood Glucose Monitor	**Addition of an alternate test site.**	**Yes, this is a significant change.**
Automated ELISA Analyzer	**Addition of a new analyte to be tested on a system (for example [e.g.] HBsAg).**	**Yes, this is a significant change.**

Changes in Materials		
All Devices	**A change in supplier or vendor of the material , but the material meets the manufacturer's previously reviewed acceptance criteria.**	**No, this change is not significant.**
Peripherally Inserted Central Catheter (PICC)	**Introduction of a colourant change into the insertion hub of a PICC that is part of the fluid path for fluid administration or withdrawal from a patient.**	**Yes, this is a significant change.**
Peripherally Inserted Central Catheter (PICC)	**Introduction of a colourant change into the flush port of a PICC. The flush port is an access port for flush syringes for IV line clearance or volume block and is not intended to be used for fluid administration or withdrawal from a patient.**	**No, this is not a significant change.**
Cardiovascular Catheter	**A change of material to a cardiovascular catheter that comes in contact with body tissue (e.g. change to/from polyether block amide (PEBA) , Polyamide or polyether ether ketone (PEEK).**	**Yes, this is a significant change.**
IVDD	**Change in magnesium stearate from an animal to vegetable source in a reagent of an IVDD kit, with no change in performance specification.**	**No, this is not a significant change.**
IVDD	**Change(s) to the formulation of reagents in test kits that result in a change to the stability claim.**	**Yes, this is a significant change.**
IVDD	**Change from a liquid to solid reagent; change from an RIA**	**Yes, these are significant changes.**

	to a non-RIA; change from immunofluorescence to ELISA; changes in the source or type of antibody that are likely to produce a change in antibody specificity, affinity or purity; or changes in the conjugate, antigens, primers or substrates.	
IVDD	**A change in the preservatives or the formulations of existing materials that does not affect the performance characteristics or lead to labelling changes.**	**No, this change is not significant.**
IVDD	**A change to the sample preparation, such as the inclusion of a stabilizer for an IVDD that is intended to simplify preparation requirements or increase sample stability.**	**Yes, this is a significant change.**
IVDD	**Addition of sodium azide a preservative to a reagent of the kit.**	**Yes, this is a significant change.**
Changes to Labelling		
All Devices	**The deletion of a contraindication, such as "not for pediatric use." Other examples would be deletion of the contraindication against lip augmentation for a dermal filler or removal of the contraindication against the use of a dental implant in patients who smoke.**	**Yes, this change is significant.**
All Devices	**A labelling change to include additional languages, other than French or English required in other regulatory jurisdictions.**	**No, this change is not significant.**

Dental Implants	**Deletion of a contraindication**	**Yes, this is a significant labelling change, including concurrent changes to the warnings.**
Dermal Filler	**Deletion of potential adverse events such as granuloma formation**	**Yes, this is a significant change.**
Percutaneous Aortic Valve	**Introduction of an additional warning to state that the device could embolize if not deployed completely and confirmed under fluoroscopy.**	**No, this is not a significant change.**
Stent Graft	**Modification of the indications for use to exclude femoral implementation, but this was previously indicated. The exclusion of an indication for use pertaining to safety and effectiveness must be identified as a contraindication.**	**Yes, this is a significant change.**
Radiofrequency Generator	**The radiofrequency generator is approved for use with licensed radiofrequency probes for the indication of creating radiofrequency lesions in nervous tissue. Another mode is activated in the generator to be used with other licensed radiofrequency probes that are approved for use in the intervertebral disc to coagulate and decompress disc material.**	**Yes, this is a significant change.**
Radiofrequency Probe	**The radiofrequency probe is indicated for ablating nervous tissue (used peripherally). The probe is now to be used in the central nervous system (e.g. brain).**	**Yes, this is a significant change.**

Changes to Sterilization		
Sterile Medical Devices	**Changes the inner sterile wrapper or the sterilization process**	**Yes, these are significant changes.**
Sterile Medical Devices	**Changing contract sterilizers (with no change to cycle parameters); the method of validating the process remains the same.**	**No, this is not a significant change.**
Sterile Medical Devices	**Changes that reduce the sterility assurance level SAL) to less than 10^{-6}.**	**Yes, this is a significant change.**
Sterile Medical Devices	**A change from biological indicator to parametric release.**	**Yes, this is a significant change.**
Sterile Medical Devices	**Change from a pre-blended sterilant (EtO and CHCs) to EtO post-blended with nitrogen. The ultimate concentration of EtO in the sterilizer is the same in both cycles.**	**No, this is not a significant change.**
Sterile Medical Devices	**A change from using Air (mixture of 80% Nitrogen and 20% Oxygen) to pure Nitrogen in the aeration process to avoid explosive gas mixtures.**	**No, this is not a significant change.**
Sterile Medical Devices	**A change in air-flow or heating, ventilating and air conditioning (HVAC) systemto the manufacturing environment, where the sterilization facility is physically and environmentally segregated from the manufacturing line**	**No, this is not a significant change.**
Double Pouched Sterile Devices	**A change to the packaging where a double pouched sterile device is put into a new**	**Yes, this is a significant change.**

	single pouch.	
Single Pouched Sterile Devices	**A change to the packaging is made where a single pouched sterile device is put into a new double pouch.**	**Yes, this is significant change.**
Changes to Software		
All Devices	**A change in computer software affects the colour coding of a visual display on a monitor, without any additional informational or decisional changes. There is a commensurate change in the colour key that is displayed on the monitor and/or in coloured product labelling, such as in the user manual or quick reference guide.**	**No, this is not a significant change.**
Programmable Medical Device	**A change in the operating system from Linux to Windows XP, but the operation of the software itself is not altered.**	**Yes, this is a significant change.**
Central Monitoring System	**Workflow change resulting in different order of monitoring patients**	**No, this is not a significant change**
Programmable Medical Device	**A change in the operating system version (e.g. Service Pack 1 to Service Pack 2), but the operation of the software itself is not altered.**	**No, this is not a significant change**
Automated ELISA Analyzer	**New version of the software that affects the calculation of the cut-off.**	**Yes, this is a significant change.**
Interpretive electrocardiogram (ECG) monitor	**The addition of new features or software applications.**	**Yes, this is a significant change.**
EtO Sterilization Unit	**A software upgrade that does not impact the cycle or sterilization assurance level, but does use a new platform,**	**No, this is not a significant change, as it is a change to the software of**

	monitors additional parameters and introduces new alarms that were not previously detected.	**manufacturing equipment.**
Flow Cytometer	**Software changes that allow for enhanced definition and clarity to the colour monitor and colour printout.**	**No, this is not a significant change.**
Insulin Pump	**Software changes that allow for wireless communication with compatible (continuous) blood glucose monitors.**	**Yes, this is a significant change.**
Electrocardiogram	**Addition to software of an early warning alarm to signal a potential cardiac event such as atrial fibrillation.**	**Yes, this is a significant change.**
Electrocardiogram	**Change in software that provides or adds a visual on-screen alarm to an existing audible alarm.**	**No, this is not a significant change.**
Blood Glucose Monitor	**A software change that allows an end-user to download historical information for trending purposes to a personal computer.**	**Yes, this is a significant change.**
Blood Glucose Monitor	**A software changes that allows for downloaded historical data to be grouped to different parameters (e.g. by time of day, month, pre-selected dating period).**	**No, this is not a significant change.**
Blood Oxygen Monitor	**A software change that allows the monitor to also report blood CO_2 concentrations.**	**Yes, this is a significant change.**
Blood Oxygen Monitor	**A software amendment that allows for the healthcare professional to select and/or change the pre-existing units of measure (e.g. $\%O_2$ and other).**	**No, this is not a significant change.**
X-ray Lung Nodule Assessment Software and Digital	**An X-ray Lung Nodule Assessment Software is used along with a Digital**	**Yes, this is a significant change.**

Radiography System	**Radiography System to support physicians in the visualization, identification, evaluation and reporting of pulmonary lesions/nodules in chest images. An algorithm change improves the detection rate for small nodules.**	
Diagnostic X-ray System	**The system does not allow printing in all formats. The system software is updated to allow paper-printout in A3 and colour format.**	**No, this is not a significant change.**