Guidance on how to interpret ‘significant change’ of a medical device

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Health Products

Table of Contents

Overview

Purpose

This document provides guidance on how to interpret “significant change” as defined in the Medical Devices Regulations. Its purpose is to help manufacturers determine whether a proposed change to a Class III or IV medical device licence is significant and requires them to submit an amended medical device licence application before implementing the change.

The guidance presents the types of changes included in the regulatory definition of significant change, along with detailed examples, so that manufacturers may interpret and apply the regulations consistently.

Scope and application

Section 34 of the regulations describes changes that require the manufacturer to submit a medical device licence amendment application. This includes when a significant change is proposed to a licensed Class III or IV medical device in accordance with subsection 34(a) of the regulations.

You should also consult this document for proposed changes to a Class II medical device that’s intended to be used with a separate Class III or IV medical device. When a change may affect the safety and effectiveness of the Class III or IV medical device, you may have to submit an amendment application for the higher-risk device before implementing the change in the Class II device.

Specific types of changes included in the definition of significant change in the regulations are presented, along with related examples, to help you understand the difference between a significant and non-significant change. A modification to a medical device may involve changes to its design, function, safety, manufacturing, packaging, finishing or labelling. The examples provided are for illustration purposes only and may not apply in all cases. It’s not feasible to describe all possible changes that could be made to a medical device.

This guidance **does not apply** to medical devices authorized under Part 1.1, in the context of an urgent public health need. Information submitted in applications made under Part 1.1 cannot be used to support a change in a medical device licence under Part 1.

For amendments to authorizations under Part 1.1, refer to the Guidance on Medical devices for an urgent public health need. If you are not sure whether your authorization under Part 1.1 is a significant change under section 68.13(a) of the regulations, email us at: meddevices-instrumentsmed@hc-sc.gc.ca.

This guidance does not apply to drug-medical device combination products that are subject to the Food and Drugs Regulations. However, the guiding principles in this document may help you determine if you should submit additional medical device-related evidence before you market a combination product for which there is a proposed change to the medical device components. This guidance does apply to combination products subject to the Medical Devices Regulations.

For more information on drug-medical device combination products, consult:

- Policy on drug/medical device combination products

Policy objectives

Our objective is to support consistent and predictable regulatory decision-making by providing guidance on Health Canada's interpretation of "significant change". This will help manufacturers identify when a licence amendment is required. It will also help ensure that changes that may affect the safety, effectiveness or quality of Class III and IV medical devices are reviewed by Health Canada before implementation.

Policy statements

When a proposed change to a Class III or IV medical device licence is a significant change, you must submit a medical device licence amendment application and obtain an amended licence before you can market or sell the modified device in Canada.

For guidance on the safety and effectiveness evidence required in such an application, consult the applicable Guidance documents for medical devices.

In some cases, a proposed change to a medical device may impact the structure of the current licence and require a new licence application be submitted rather than an amendment.

For more information on how your proposed changes may affect your licence structure, consult:

- Guidance for determining medical device application type

All changes to the medical device, including changes to labelling, must be documented in your quality management system. After consulting this guidance, if the changes are not deemed significant, you must still report changes related to information and/or documents submitted with your medical device application to Health Canada at annual renewal time. We suggest that you itemize these changes in a table and provide a brief rationale as to why the change is not considered significant.

If you are unable to determine whether your proposed change is significant after going through all applicable sections, you should contact the Medical Devices Directorate by email at meddevices-instrumentsmed@hc-sc.gc.ca for additional information. Provide a complete description of your proposed change as well as why you were unable to determine the significance of your change.

Note about guidance documents in general

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They 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 always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, effectiveness or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

General principles

Overview of the general principles

A significant change under section 34 of the Medical Devices Regulations is a change that could reasonably be expected to affect the safety or effectiveness of a licensed Class III or IV medical device.

All devices listed on a Class III or IV licence will be reviewed in accordance with section 10 to 20 of the regulations.

A proposed modification to a Class II licence may require a Class III or Class IV amendment before the proposed modified device is sold if the:

- device on the Class II licence is intended to be used with a separately licensed Class III or IV medical device **and**
- proposed modification may impact the safety or effectiveness of the devices when all components are used together as intended

Any change made to a device, including changes to labelling and packaging, is likely significant if:

- the safety or effectiveness of the device could be affected
- the change was made in response to new information that alters your understanding about the safety or effectiveness of a medical device
- a new, previously unidentified hazard or hazardous situation was identified
- the likelihood of a known hazard occurring has changed
- the severity of an adverse consequence has changed
- a risk control measure has been added, removed or relaxed

If you are proposing multiple changes, you should consider each change individually and evaluate the combined impact the changes have on the device.

A determination that a change is significant may occur when:

- one of the proposed modifications is determined to be a significant change **or**
- the collective impact of any combination of proposed changes is deemed to be significant

In general, a determination that a change is non-significant may occur when:

- a risk assessment of the proposed changes concludes that
    - any new or modified risks are negligible **and**
    - the probability of introducing unintended consequences is negligible

In all cases, if any change is determined to be significant under any section of this guidance document, the final determination should be that an amendment application is required.

For significant changes, you must submit an application to amend your medical device licence as per section 34(a) of the regulations.

Where to start

The first step is to determine which section best describes your proposed change.

The type of change that best describes your proposed change should serve as your starting point in determining significance. This is only a starting point as there may be multiple sections that apply to your proposed change.

To help determine whether a change is significant:

- consider this general principles section as well as the applicable descriptions of the types of changes
- consider the impact the change may have on the patient or intended users
- consider if any specifications have changed
- determine whether the change, prior to testing, could have reasonably been expected to affect the safety, quality or effectiveness of the device, in either a positive or negative way
- consider the results of a risk assessment specific to the change
- consider whether data supporting the modified device can be interpolated from existing datasets
- consider the need for and results of verification and validation testing

Use this guidance document to assess each proposed change on its own, as well as the combined impact of all the changes, when you are:

- considering several simultaneous changes in the evolution of a licensed device
- modifying 1 or more component parts of a medical device licence as a system, test kit, group, family or group family

It may be useful to compare the proposed changes side by side with the current licensed device.

Using risk assessments

A risk assessment should be incorporated throughout the process of assessing the significance of a change and again as a final step.

A risk assessment is especially helpful in determining whether a change is significant in situations where the descriptions provided in this guidance may not:

- explicitly address the specific change **or**
- initially lead to a determination that the change is significant

The risk assessment should identify and analyze new risks, as well as changes to existing risks, that may result directly or indirectly from the proposed change.

A proposed change intended to improve the safety of a device may unintentionally introduce new risks or alter existing ones that could compromise the safety or effectiveness of the device. The risk assessment should therefore consider the potential for such unintended consequences.

Examples of possible unintended consequences that could be identified by a risk assessment:

- A delivery system is modified to prevent premature deployment, which unintentionally introduces a new feature or component that could damage or shorten the useful life of other components, or cause a failure itself.
    - For example, the device fails to deploy or only partially deploys.
- An alarm may be added to warn of an adverse event, but the sound or visual cue may resemble another alarm and thus may be misinterpreted. It may also trigger too

frequently, leading to alarm fatigue and reducing the likelihood that users respond to higher-priority alarms.

A risk assessment may conclude that the change is likely non-significant if:

- no part of the change has been assessed as being significant **and**
- the probability of introducing unintended consequences is inherently negligible by design, based on the nature of the change

Using the four-corner principle

As a general principle, when a new modification to a device completely falls within the scope of existing licensed devices, the change is generally considered to be non-significant. This principle is based on the "four-corner testing" paradigm, which refers to:

- a method of assessing the extreme or most important aspects, features and characteristics of a system **and**
- how it performs or behaves in a variety of settings, situations or environments

In this paradigm, the 4 corners represent the most extreme conditions or features of a given system or of the environment in which it may be used.

For example, if a device is a tube available in different lengths and diameters, the 4 corners would be the:

1. longest length with the largest diameter
2. longest length with the smallest diameter
3. shortest length with the largest diameter
4. shortest length with the smallest diameter

Testing of these 4 corners would represent the extremes of the licensed models of the device. It would cover the full spectrum of expected performance for devices with lengths and diameters within the bounds defined by these four corners when used for the same indications for use.

The change is likely non-significant when:

- a proposed device modification does not introduce a feature or condition that exceeds the extremes of existing licensed devices **or**
- the extremes of the clinical environment in which they may be used

The change may be considered non-significant if the scope of the change:

- can be fully verified and validated based on test data that was previously submitted as part of a licence or licence amendment application **and**
- is fully applicable to the current licensed devices

Examples of a non-significant change:

- The length of the changed device is between the length of 2 existing licensed devices under the same licence, with all other features being the same.
    - You must verify that this change does not alter the safety or effectiveness of the device and that performance remains consistent with the existing range of devices.
- The indications for use have been narrowed to a subset of previously licensed and explicitly stated indications accepted during pre-market review of the subject devices.
    - This change must not have been made based on new data indicating the device is unsafe or ineffective for the previously licensed indications for use.

Examples of a significant change:

- The size of device is larger than the current range of licensed devices.
- The indications for use have been expanded to include a new clinical use case.

As an exception to this rule, if the behaviour of the device is difficult to predict based on the behaviour at the 4 corners, then the change is significant. This may occur:

- when performance could potentially be altered significantly based on minor changes within the 4 corners **or**
- when localized effects, such as a natural frequency effect, within the 4 corners can result in extreme outcomes

Examples of such a significant change:

- The size of the device is between 2 existing licensed device sizes where performance of the device is a non-linear or unpredictable within the 4 corners.
    - Such changes are significant because the performance of the device cannot be adequately predicted from existing data and device durability may be highly sensitive to changes in size.
- Magnetic resonance (MR) conditional claims have been modified or newly introduced for an active medical device.
    - Such changes are significant because the performance of these types of devices within an MR environment cannot be adequately predicted from existing data. This is because non-linear effects and natural frequency effects may occur within the MR environment.

Design verification and validation

Design verification testing ensures that a device meets its design specifications. Most device design changes will require design verification testing.

A change to a device is likely significant if design verification testing:

- produces unexpected results
    - in such cases, the risk assessment should be re-evaluated to determine if the change could affect the safety or effectiveness of the device
- differs from the verification testing conducted for a previous application, particularly when the change to the device is the reason new or modified testing is required
    - differences in testing may include changes to test methods, protocols or acceptance criteria

Design validation testing demonstrates that the device performs as intended clinically. The need for validation testing usually indicates that the change made to the device is significant. However, the absence of validation testing does not necessarily mean the change is non-significant.

Types of changes

Changes to manufacturing processes, facilities or equipment

For the purposes of this section, a manufacturing change impacts how a device is made but does not intentionally change the design of the device, its packaging or labelling material.

Examples of manufacturing changes include:

- changes to the component formation process
    - for example, switching from an extruded to a machined component
- altering manufacturing machine tolerances
- replacing equipment used to perform a manufacturing function
- moving manufacturing to a new facility

A change to the manufacturing process, facility or equipment can impact the safety or effectiveness of a device. You should assess the impact of all manufacturing changes on the device specifications, performance and material properties. These changes should also be evaluated using other relevant sections of this guidance document.

If a change to the manufacturing process, facility or equipment involves changes to the sterilization process, refer to the section on changes to sterilization.

Tolerances that have been increased to allow for more variation in the end product likely represent a significant change, as this may impact device performance.

Examples of changes that are likely non-significant include:

- changes that tighten specifications within the existing range of licensed specifications for the same device, model or component on the licence where the mean value is not substantially altered
- increases to the tolerance ranges, if the impact of the change is fully verified and validated from the information previously submitted and reviewed by Health Canada for the same licensed device
- changes to the manufacturing process, facility or equipment that do not impact the device specifications, performance or materials and for which incoming inspections to evaluate the material provided by the supplier have not been changed

- the addition of a new manufacturing facility when the:
  - manufacturer's name and address on the device labelling stays the same **and**
  - new facility has the same manufacturing process and equipment of the same specifications **and**
  - new facility is not a new sterilization facility or new abattoir for animal-derived materials
    - For more information, refer to the section on changes to sterilization and the section on changes in materials for non *in vitro* diagnostic devices

For combination products regulated as medical devices, changes involving active pharmaceutical ingredients (APIs) require special consideration due to increased sensitivities associated with API production and application.

Changes to the manufacturing process of a combination product that involve APIs are often significant. For this reason, we recommend that you contact the Medical Devices Directorate by email at meddevices-instrumentsmed@hc-sc.gc.ca for specific guidance on all changes to manufacturing process, site or specifications for the API of a combination product.

Table 1: Examples of changes to manufacturing processes, facilities or equipment

Device	Proposed change	Significant or not significant
Drug eluting implant	A change to the location of a manufacturing site where the excipient or drug coating is applied to or integrated onto or into the device.	Significant A change in the location of the manufacturing site for the coating could affect the device's safety or performance. The change in manufacturing site location may also impact quality system requirements.

Device	Proposed change	Significant or not significant
Implantable 3D printed devices	Changes to additive manufacturing processes including equipment, raw materials or post-printing processes of the device.	Significant A change in the manufacturing process of 3D-printed devices involving a change in equipment, starting materials, or post-printing process is critical to device characteristics and could affect the device's safety or performance. For more information, consult the guidance document Supporting evidence for implantable medical devices manufactured by 3D printing
Medical device containing animal or human-derived tissue materials	Change in animal or human tissue supplier.	Significant A change in supplier could impact biological safety requirements for animal or human-derived tissue materials, performance or risk profile of the device. For details, refer to the section on changes in materials for non *in vitro* diagnostic devices.

Device	Proposed change	Significant or not significant
Devices sold as non-sterile	Packaging changed from 1 variant of polyethylene to another due to supplier rationalization or cost-saving measures. Verification and stability testing shows integrity has not been compromised.	Not significant A change in supplier of the packaging material, given no impact on packaging performance and packaging is not sterile, should not affect the overall safety and effectiveness profile of the device.
Catheters	Change in supplier that extrudes the polymer tubing with no change in finished product performance specifications.	Not significant A change in supplier should not affect the device's safety and performance as the finished product specifications are unchanged from that previously considered during pre-market review.
All devices	A change in non-biological material supplier where the design or performance specifications of the finished device are not impacted and the material type, formulation, chemical composition or processing have not been changed.	Not significant A change in the material supplier should not affect the device's safety or performance if the material specifications are unchanged and the device continues to meet previous acceptance criteria.

Changes to manufacturing quality control procedures

For the purposes of this section, a manufacturing quality control change impacts oversight of the manufacturing steps, but does not intentionally change the design of the device, its packaging or labelling material.

Examples of manufacturing quality procedure changes include:

- changes to test or inspection criteria
- alterations to test methods
- adding or deleting a tested or inspected parameter
- changes to statistical rationale or sample size
- changes to acceptance quality limits (AQL)
- changes to validation endpoints
- increasing or decreasing required sterility assurance level (SAL)

Changing or adding new testing or inspection activities for incoming materials, in-process materials and final products is not a significant change if the specifications or acceptance criteria have not been loosened and AQLs have not increased. On the other hand, removing or modifying these activities where the result is that specifications or criteria are loosened or AQLs are increased is a significant change.

The following changes are often considered significant:

- changes to quality control inspections or tests used to control the quality, purity or sterility of materials
- changes that could affect the specifications of the finished device or its components, including its packaging

However, if adding or modifying the inspection or test method results in equivalent or improved assurance of reliability, then the modification would not be deemed a significant change.

Table 2: Examples of changes to manufacturing quality control procedures

Device	Proposed change	Significant or not significant
All devices	Modification or removal of a test that characterizes the final product or its performance (for example, bending test for a metal component)	Significant Removing or modifying a test currently used to identify design specifications or performance following device manufacture may compromise the quality of the final product.
All devices	Change in design specifications of a device to accommodate a loosening of acceptance criteria as a result of a change in supplied parts or materials.	Significant The change involves loosening acceptance criteria and design specifications of the final product and may increase acceptance quality limits.
All devices	Reduction in pre-delivery inspection criteria for a patient contact material due to change in supplier of the identical material where there is no change to design specifications	Significant Quality control steps have been reduced and may result in negative impacts on the final product.

Device	Proposed change	Significant or not significant
All devices	An in-process inspection of component length is change to 100% inspection of component length later in process.	Not significant The inspection activities do not alter the specifications or performance of the device and acceptance quality limits have not increased.

Changes in design

Changes in design range from minor design specification or 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.

Examples of design changes can include modifications to the:

- device's control mechanism
- device's operating principles
- device's design specifications
- device's components or accessories
- human factors of the patient or user interface

Control mechanism

A control mechanism refers to the means by which a device's actions are directed or its output is regulated. Control mechanisms can be complex. Any modification to them has the potential to alter how the device functions. Such changes may affect the device's risk profile, safety or effectiveness. Therefore, changes to the device's control mechanisms are considered significant.

Operating principles

Operating principles are the means by which a device produces or brings about an intended or appropriate effect. Changes to operating principles are considered significant.

For more information on operating principle changes that include software, refer to the section on changes to software.

Design specifications

Changes to design specifications can include modifications to the:

- physical characteristics such as shape, size, dimensions or materials, including non IVDDs and IVDDs
- performance or technical specifications
- patient or user interfaces
- software or firmware updates
    - for more information, refer to the section on changes to software
- precision, accuracy, sensitivity, specificity or stability for IVDDs

A change to design specifications may be significant if it affects at least 1 of the following 3 factors:

1. indications for use or intended use
2. requirements to have clinical data
3. risk profile of the device

1. Indications for use or intended use

Changes to design that affect the indications for use or intended use are considered significant. Such changes may impact the:

- target patient population
- for example, elderly or pediatric patients
    - target anatomical site or area
- target disease, disease state or condition

2. Clinical data

Changes to the design specifications that require new clinical data to demonstrate and validate the safety and/or effectiveness of the device are significant.

3. Risk profile

A design change may introduce new hazards or hazardous situations, alter the severity or probability of harm, or require new risk-mitigation measures. A new risk assessment should be conducted for any design change. The risk assessment should identify any new risks.

If the risk assessment finds that the change could alter the safety or effectiveness of the device, the change is significant. However, a change is not significant if the risk assessment and its conclusions remain unchanged by the design change and the device performance is unchanged compared to the design that underwent pre-market review.

Components or accessories, including Class II devices

A change in device design may result from modifications to accessories or devices intended to be compatible with a licensed Class III or IV device, regardless of if they are licensed together or separately. This includes those listed under a Class II licence.

Adding new components or changing the design of device components or accessories used with a Class III or IV device are considered significant changes if they:

- affect the safety or function of the device as a whole **or**
- substantially alter how the user interacts with the Class III or IV device through the operation of the modified or newly added design of the components or accessories **or**
- could cause the device to be used in a new way
    - for example, new workflow, new patient population, new indication

Modifying an existing component or accessory or adding a new component or accessory that is intended to be, or labelled to be, compatible with a Class III or IV device is a significant change if:

- this addition or modification may impact the safety or effectiveness of the assembled combination of devices, components or accessories when used as intended.

This applies regardless of the classification of the component or accessory, or whether all parts are on the same licence or licensed separately. An application to amend the associated Class III or IV device is required. The application must include a clear description of the change, as well as evidence verifying the safety, effectiveness and compatibility of the modified or added components or accessories with the Class III or IV device.

For more information, refer to the section on Class III and IV amendments for compatible Class II devices.

Human factors of the patient or user interface

A design change that affects how the device is used or how it interacts or interfaces with the patient or user is generally considered significant.

Examples of such changes include:

- changes to the display or layout of a control panel or graphical user interface (GUI) if used for device control or risk mitigation
- changes to how the device interacts with the patient or user, particularly when the information exchanged is necessary for monitoring device performance or function
- changes to the design of a surgical tool or delivery system that modify how the surgeon operates or manipulates the device

Cosmetic or aesthetic modifications, such as those made solely for appearance or user comfort, are generally not significant if they do **not** affect device function, use, clinical performance, safety or effectiveness.

Table 3: Examples of design change

Device	Proposed change	Significant or not significant
All devices	New foot switch (where there was not one before) added to an electrosurgical generator or other device, and corresponding software added to the operating console.	Significant Change in the way the device is operated can impact the usability profile. Changing software is also a significant change.
Non-active surgically invasive devices	Adding a longer hip prosthesis meant for a revision patient population. or A smaller fracture fixation screw that can be used in a different anatomical location from the licensed devices.	Significant Change in the design characteristics allows for additional or broader indications for use.
Catheters	Change to the cable design and grip of a steerable ablation catheter, which results in improved deliverability and improved procedural times.	Significant Change in design impacts performance and usability.

Device	Proposed change	Significant or not significant
Endocardial lead	Additional polymer support clip added to prevent the electrical connection from becoming dislodged and to increase the axial retention forces.	Significant Additional component changes risk profile.
Hemofiltration system, including software controls	New component, combined filter and disposable cartridge added.	Significant Addition of new components may impact performance and software controls.
Transurethral thermal system for treating benign prostatic hyperplasia	Software changed to provide automatic control of ramping power, respond to elevated rectal temperatures automatically and adjust power.	Significant Change to control mechanism.
Metallic biliary stent for treating malignant strictures	Two new stent lengths added that are outside the range of previously licensed stent lengths on the same licence.	Significant Dimensions outside of approved range are not supported by the four-corners principle or previously reviewed evidence.

Device	Proposed change	Significant or not significant
Total hip system	New bearing surface added.	Significant Design change could impact risk profile or performance
Acetabular cups	Change in design to give additional flexibility to implanting surgeons. More holes added to the cups.	Significant Design change affects mechanical properties and thus risk profile or performance.
Bone void fillers and putty	Amount of cancellous bone material in the filler increased.	Significant Change in design specification can affect performance.
Anaesthesia machine	Change in the sensor controlling the fresh air proportions.	Significant Change in device design can impact performance.
Automatic implanted cardiac defibrillator	Internal components, including the capacitors, telemetry coils, batteries and transformers, altered to improve how the device operates.	Significant Changes could impact performance and risk profile.

Device	Proposed change	Significant or not significant
Cardiac pacing leads	Adding 2 or more electrodes, or a new anchoring mechanism that can result in new indications for use and enhance performance claims.	Significant Change to indications for use and device performance.
Pacing lead	Size of the wire diameter reduced to decrease the overall lead diameter to facilitate introduction into the vessel.	Significant Change in device dimension for which there was not previously a smaller diameter. The four-corner principle cannot be applied if evidence for representative devices did not previously include the new model's dimension (not within the 4 corners).
Pacing lead	A new lead length is added that lies in between two licensed leads, and it includes the same MR conditional claims as the existing licensed pacing leads.	Significant Due to the 'antenna' behaviours of a pacing lead in an MR environment, there are non-linear and natural frequency effects that cannot be predicted based on a four-corners principle to the analysis.

Device	Proposed change	Significant or not significant
IVDD test kit	Sample matrix for an IVDD test kit changed from a venous blood sample to a dried blood spot.	Significant The new sample collection and preparation procedure could impact performance.
Clinical chemical analyzer	Throughput changed.	Significant Changes in throughput can impact the performance of the assay
Clinical chemical analyzer	Test volume changed.	Significant Changes in test volume can impact the performance of the assay.
Clinical chemical analyzer	Full automation changed.	Significant Changes in a fully automated system may impact the risk profile

Device	Proposed change	Significant or not significant
Automated ELISA analyzer	New analyte added (for example, Hepatitis B surface antigen).	Significant The display will change to accommodate a new analyte. This can impact the ability of users to adequately interpret the results.
IVDD test kit	The blood collection method for a point-of-care IVDD changes from a capillary draw to a mechanical draw pipette.	Significant Changes in the sample collection procedure can impact the ability of users to adequately collect the sample and potentially impact the performance of the test.
IVDD	Changing an immunofluorescence-based assay to an enzyme-linked immunosorbent assay (ELISA).	Significant This is a change in operating principle.
Blood glucose monitor	A new control added.	Significant Adding a control may make the system more complex for users and impact test performance.

Device	Proposed change	Significant or not significant
Blood glucose meter	Sample volume reduced by changing the electrode layout, which reduces the test strip sample chamber volume.	Significant Reducing sample volume may impact the ability of users to adequately perform the test as well as test performance.
Blood glucose meter	Alternate sampling location added (for example, abdomen).	Significant Different sampling locations may introduce biological variations in samples collected and impact the ability of users to adequately collect and prepare the samples, potentially impacting test performance.
Mechanical ventilator	Changing the design from a pneumatic to electronic control.	Significant This is a change in the control mechanism.
RF generator/ Any user interface	Changing from an analog control to a digital controller on a RF generator.	Significant This is a change in the control mechanism.

Device	Proposed change	Significant or not significant
Active device	Switching the energy input source between AC, DC or battery.	Significant This is a change in the operating principle and energy source.
Ablation device	Changing output from microwave to radiofrequency.	Significant This is a change in the operating principle and will have different benefit-risk considerations
Patient/clinician controller	Changing from a wired to wireless communication or changing between types of wireless communication such as WIFI to Bluetooth.	Significant This is a change in operating principle and may impact effectiveness or safety of the device.
Cardiovascular stent	Changing the length or diameter of a cardiovascular stent so it can be placed in different arteries, which may introduce or imply additional indications for use (whether explicitly claimed in the labelling or not).	Significant The benefit-risk profile of the previous clinical scenario may be different from new use cases due to changes in dimensions.

Device	Proposed change	Significant or not significant
Transcatheter heart valve	Adding intermediary sized value to the licence.	Significant This may require new clinical evidence due to non-linear considerations.
Implantable device	Reducing the size of an implant currently intended only for adults such that it can fit a wider range of patient population.	Significant This change in design impacts the implied patient population and would require clinical evidence to be updated to reflect a new benefit-risk profile.
Bone cement	Change in viscosity to reduce the risk of extravasation.	Significant This change alters the risk profile and creates new risks due to the new handling properties.

Device	Proposed change	Significant or not significant
Catheters	Change to the grip of a steerable ablation catheter to improve comfort for the health care professional or improve the appearance of the device without changing its functionality or any critical forces that could be applied and felt (tactile) by the user.	Not significant Cosmetic change that will not impact usability.
Metallic biliary stent for treating malignant strictures	Two new stent lengths added that are between the previously licensed stent lengths on the same licence, with no other differences.	Not significant Dimensions are within previously approved range, with no other changes and are supported by four-corners principle.
Patent foramen ovale (PFO) closure device	An 18-millimetre (mm) PFO closure device added to a licence that includes a 16-mm and a 20-mm PFO closure device. Basic design and delivery system are the same.	Not significant Dimensions are within the previously approved range with no other changes and are supported by four-corners principle.

Device	Proposed change	Significant or not significant
IVDD	Changes in methods such as specimen pretreatment, incubation times and temperatures, which did not result in modifying performance characteristics or a labelling change.	Not significant Device performance is within existing claims, labelling remains unchanged and the risk profile of the device is unchanged.
Transcatheter heart valve	Modifying the design of a skirt on the valve to reduce the risk of paravalvular leakage using the same design already added to a valve on the same licence.	Not significant This change does not alter the risk profile if it is supported by the same body of evidence previously submitted for pre-market review for the subject licence.

Changes to sterilization and sterile barrier packaging

Changes that could affect the effectiveness of the sterilization process or the safety or effectiveness of the sterilized device are considered significant. This is regardless of whether the sterilization process is during manufacturing or by the end user. The same considerations should also be applied if a device requires disinfection for safe use. Given that it's impossible to determine by inspection if a device is sterile or adequately disinfected, this must be confirmed through a validated process.

Medical devices are considered sterile when the sterility assurance level (SAL) of 10^{-6} or better is demonstrated. The sterilization process must be verified and validated, and its ongoing performance routinely monitored.

Examples of significant sterilization changes are where the:

- manufacturing process, environment or device material may introduce an organism that is more difficult to kill compared to the challenge organism previously used in sterilization validation testing
- manufacturing process, environment or device material increases the bioburden above the maximum bioburden level previously validated in sterilization validation testing
- device design introduces a feature or alters existing features that result in a new worst case more-difficult-to-sterilize location for existing sterilization validation
- device material is more difficult to sterilize or increases sterilant residuals
- quality control verification and validation processes are changed, such as introducing or removing parametric release or changing the sterilization dose auditing method
- type of sterilization method is changed during manufacturing or recommended to end user in labelling
- critical cycle parameters (such as ethylene oxide gas concentration or radiation dose) are changed
- dose delivery is changed (such as changes in loading density or configuration)

In general, any change that could trigger a new or increased risk is a significant change.

Non-significant changes would be those limited to adding a new facility, chamber or equipment that uses the same sterilization method and critical cycle parameters. For example, EO gas concentration or radiation dose and validating to a SAL of 10^{-6} using a Health Canada-recognized standard, such as:

- ISO 11135 or ISO 11137 **or**
- an identical international version of these standards like BS EN ISO 11135 or BS EN ISO 11137

Adding a new test acceptance criteria or test method to the existing process to provide the same or better assurance of sterility, reliability or similar safety aspects is generally considered a non-significant change.

Using a sterilization method that does not adhere to recognized standards (refer to Health Canada-recognized standards) may impact the expected sterility assurance level of the

device. For changes involving **novel sterilization technologies**, you should contact the Medical Devices Directorate for guidance at meddevices-instrumentsmed@hc-sc.gc.ca.

A change in manufacturing facility is considered significant if it introduces a new or more challenging organism or results in a higher bioburden level that was not previously validated in the sterilization process. This applies even when the sterilization cycle parameters remain unchanged, as the validated worst-case conditions are no longer assured.

Changes to sterile barrier packaging

Packaging changes must be assessed for their potential impact on sterilization. In general, any modifications to packaging characteristics (for example, material type, size, shape, seal width or configuration, such as in the outer packaging, loading density) is likely significant if it could affect:

- absorption or penetration of the sterilant
- sterilant residual levels (where applicable)
- the overall effectiveness of the sterilization process
- the safety or integrity of the sterile device
- package seal strength and sealing process parameters

Compatibility between the packaging material and the sterilization process must also be assessed, as changes may alter the performance or reliability of the packaging.

Changes to previously approved cycles or configurations

A change to the sterilization method or packaging of a sterile medical device is likely not significant if:

- it has already undergone successful pre-market review in a previous new or amendment application for a similar device by the same manufacturer **and**
- all of these conditions are met:
    - the device is not more difficult to sterilize than the previously licensed comparator device
    - the interaction between the device and the proposed packaging does not introduce greater risk to the integrity of the sterile barrier

- the devices are made of identical materials and have similar designs, with no new features that would create a new worst-case scenario for sterilization
- the proposed changes were explicitly represented, requested and approved in a previous new or significant change application

Table 4: Examples of changes to sterilization

Device	Proposed change	Significant or not significant
Sterile medical devices	Sterilization method changed from ethylene oxide (EO) to gamma radiation.	Significant The sterilization method is changing. This may impact device safety, effectiveness or sterilization level.
Sterile medical devices	Biological indicator changed to parametric release.	Significant The quality control verification and validation processes are changed. In addition, there is a change in the quality control mechanism
Sterile medical devices	Changes that reduce the assurance of sterility (for example, from an SAL of 10^{-6} to an SAL of 10^{-5}).	Significant The effectiveness of the sterilization process or the safety of a sterile device has changed. This change also impacts the benefit-risk profile of the device.

Device	Proposed change	Significant or not significant
Sterile medical devices	New alternate EO sterilization facility added with a proposed cycle that is identical to the currently licensed cycle in all critical parameters and uses different sterilization equipment. Some parameters such as relative humidity are adjusted due to local elevation differences. The new cycle was successfully validated using the overkill method outlined in ISO 11135.	Significant The sterilization method and critical cycle parameters have not changed but the equipment used is different.
Sterile medical devices	Irradiation dose auditing method changed from VDmax to method 1A/1B, method 2 (per ISO 11137) or vice versa.	Significant The quality control verification and validation processes have changed. There is also a change to the control mechanism of previously validated process.

Device	Proposed change	Significant or not significant
Sterile medical devices with single pouch packaging	Packaging of a sterile device changed from a single sterile barrier packaging to a new double sterile barrier packaging.	Significant The changes could affect the effectiveness of the sterilization process and the integrity and durability of the sterile barrier. The changes may impact the success of the sterilization process or influence the process on device safety or effectiveness.
Sterile medical devices with double sterile barrier packaging	Double sterile barrier packaging replaced with single sterile barrier packaging.	Significant The changes could affect the effectiveness of the sterilization process, the integrity and durability of the sterile barrier or how the sterilization process influences safety or effectiveness of the device.
Sterile medical devices	Packaging dimensions changed or protective enclosure added within the layers of sterile packaging (for example, resin).	Significant The changes could affect the effectiveness of the sterilization process, the integrity and durability of the sterile barrier or how the sterilization process influences the safety or effectiveness of the device.

Device	Proposed change	Significant or not significant
Sterile medical devices	Concentration or exposure time of EO reduced and successfully validated using a method defined in ISO 11135.	Significant The critical cycle parameters have changed. The change may impact the success of the sterilization process.
Sterile medical devices	New alternate EO sterilization facility is added with a proposed cycle that is identical to the currently licensed cycle in all critical parameters and uses the same sterilization equipment, but some parameters such as relative humidity are adjusted due to local elevation differences. The new cycle was successfully validated using the overkill method outlined in ISO 11135.	Not significant The sterilization method and critical cycle parameters have not changed.
Sterile medical devices	Airflow or heating, ventilating and air conditioning (HVAC) system in the manufacturing environment changed. The sterilization facility is physically and environmentally segregated from the manufacturing line and the device bioburden did not increase above previous level.	Not significant The bioburden did not increase above the previously validated maximum bioburden level.

Device	Proposed change	Significant or not significant
Sterile medical devices	A minor change to cycle parameters (for example, humidity, pressure, elevation).	Not significant These changes do not affect the delivered dose or sterilant residuals set out in the approved process and validation.
Sterile medical devices	Contract sterilizers changed, with no change to cycle parameters, sterilization equipment or method of process validation.	Not significant The critical cycle parameters and quality control verification and validation processes have not changed. The process validation should still apply.
Sterile medical devices	Pre-blended EO sterilant changed to EO post-blended with nitrogen where the ultimate concentration of EO in the sterilizer is the same in both cycles, with no change to the critical cycle parameters (delivered dose of EO).	Not significant The sterilization method and critical cycle parameters have not changed.

Device	Proposed change	Significant or not significant
Sterile medical devices	Change from using air (mixture of 80% nitrogen and 20% oxygen) to pure nitrogen in the aeration process to avoid explosive gas mixtures, with no change to the critical cycle parameters (delivered dose of EO).	Not significant The sterilization method and critical cycle parameters have not changed.
Sterile medical devices	A proposed packaging change previously reviewed and approved during an amendment explicitly requested the identical packaging for a similar device sterilized using the same cycle. The subject device presents no greater challenge to sterilization than the comparable device and the package materials are identical.	Not significant The change has already been reviewed and approved in a previous application for a similar device.

Changes to software

For the purpose of this section, medical device software can either be integrated into the hardware of a medical device or distributed separately. Our recommendations in this section apply to both software and firmware.

Software can be updated easily and frequently, and thus may undergo multiple changes throughout its lifecycle. Health Canada considers some of these changes to be significant.

Examples of significant software changes are those that:

- affect the function or performance specifications associated with the intended use of the device or the intended use of a compatible device whose function is controlled by the software
- introduce a new risk or modify an existing risk that could result in significant harm, including harms from unintended consequences
- create or necessitate a new risk control measure or modification of an existing risk control measure for a hazardous situation that could result in significant harm

Examples of non-significant changes, if none of the previous changes apply, are those that:

- are made solely to return the system into specification of the most recently licensed version of the device
- incorporate changes to the operating system on which the software runs, without changing the underlying software code
- are made solely to strengthen cybersecurity and do not have any other impact on the software's or the device's safety or effectiveness
- only introduce features with no medical purpose such as printing, faxing, improved image clarity, reporting format or additional language support
- only modify the appearance of the user interface, with little risk of affecting the usability, diagnosis or therapy delivered to the patient
- disable a feature that does not affect the safety or effectiveness of the device

These examples are only illustrations. All software changes should be evaluated for their potential to create unexpected software behaviour. Whether a change is significant depends on its potential impact on device safety or effectiveness. A risk assessment is recommended following any software modification.

Other examples of software changes that may or may not be significant:

- rewriting the software in another programming language is likely to be significant
- driver modifications are likely to be significant
- changes to the operating system may be:
    - non-significant if no changes are made to the application

- significant if driver changes are required or the kernel differs between operating systems
    - for example, a change in operating system family from Windows to Linux or a major Windows change from XP to Windows 10

Medical devices that use machine learning (ML), in part or in whole, to achieve their intended medical purpose are referred to as machine learning-enabled medical devices (MLMD). A predetermined change control plan (PCCP) provides a mechanism to address cases where pre-authorization of planned significant changes is needed to address a known risk. This approach can be beneficial in managing certain known risks with MLMD, such as ML system performance degradation over time due to ML model drift.

For medical devices that have been licensed with a PCCP, any significant changes made according to the authorized PCCP have already undergone review. Thus, an amendment application is not required.

For amendments to a device that are outside of an authorized PCCP, including changes to the PCCP itself, consult:

- the Medical Devices Regulations
- other relevant guidance documents in addition to this one

For more information on submission requirements for MLMDs and PCCPs, consult:

- Pre-market guidance for machine learning-enabled medical devices

Common software change types and potential unintended consequences

Software changes can come in several different forms, such as:

- infrastructure changes
    - for example, changing compilers, programming languages, software drivers
- architectural changes
    - for example, new operating system compatibility, software changes to support modified or new hardware
- algorithm changes
    - for example, modifications to the logic or calculations performed by the software
- cosmetic changes
    - for example, new logos, user interface fonts, colours
- refactoring
    - for example, improving software efficiency, structure or maintainability without changing the software behavior or functionality
- re-engineering
    - for example, reconstituting the software in a new form, replacing aging software

Cosmetic changes are often non-significant. However, the changes listed here may be deemed significant as there may be unintended consequences when executing software code in often complex software environments. For example, an operating system (OS) upgrade may:

- trigger unintended effects through the use of different drivers or kernels
- require updates to other software components to maintain compatibility

You should carefully evaluate the potential consequences of software changes to determine whether the change is significant, considering its potential impact on the safety or effectiveness of the device.

Table 5: Examples of software changes

Device	Proposed change	Significant or not significant
Software – skin cancer detection and characterization	A mobile medical app intended to detect and characterize skin cancer is enhanced by updating its model parameters. There are plans to distribute the upgraded app automatically to existing users. The change affects the sensitivity and specificity of the detection algorithm.	Significant The modification may impact clinical functionality or performance of the device.
Software – IVD device	A software modification allows an IVD device to improve sample throughput. Modifications include changes to decrease assay times by allowing for shorter sample reaction times.	Significant The shorter incubation time may affect diagnostic performance.
Software – chest X-ray application	A software application using AI-based image analysis of chest X-rays adds a model for detecting endotracheal tubes.	Significant The new diagnostic feature affects the device performance and introduces a new intended use and a new risk.

Device	Proposed change	Significant or not significant
Software – infusion pump	An infusion pump has 2 occlusion detection alarms: occlusion downstream and occlusion upstream. The software is modified to allow the user to optionally disable 1 alarm. This means the user now has the option to use 1 or both occlusion alarms.	Significant This is a change to existing risk controls in the device.
Software – operating system	A CT scanner's operating system has been upgraded to Windows 10 from Windows 7. Small infrastructure and architectural changes were made to the software to allow for compatibility.	Significant The new OS belongs to the same OS family. However, the infrastructure and architectural changes could have unintended consequences that could affect the device's performance.
Software – operating system	A blood glucose monitor has been modified to make Android and iOS devices compatible (including control of the device). Previously it had been compatible only with Windows PCs.	Significant While the underlying intended functionality of the device has not changed, the design to implement those functions needs to reflect differences between Android and iOS. Verification and validation of one does not support the other.

Device	Proposed change	Significant or not significant
Software – cybersecurity	A connection attempt limit is added to an implanted cardiac pacing device that locks access to the device following a set number of failed connection attempts. This is done to prevent unlicensed access. The change is made to strengthen the cybersecurity of the device.	Significant The change may restrict legitimate connections that are clinically important for accessing or operating the device. By reducing availability in clinical use, the change alters the device's risk profile and may adversely affect its safety and effectiveness.
Software – MLMD licensed with a PCCP	Changes to the performance limits of the device defined within the PCCP.	Significant Changes that affect the performance specifications are significant.

Device	Proposed change	Significant or not significant
Software – MLMD licensed with a PCCP	Change to the PCCP-defined change protocols that: Introduces a new risk, modifies an existing risk **or** necessitates a new risk control measure **or** modifies an existing risk control measure that could result in significant harm. This can include, for example, changes to the: • ML methods, ML architecture or ML training algorithms • reference standard or ground truth • performance monitoring techniques or triggers for evaluation	Significant Changes that introduce a new risk, modify an existing risk, necessitate a new risk control measure or a modification of an existing risk control measure that could result in significant harm are significant.

Device	Proposed change	Significant or not significant
Software – operating system	An ultrasound system's operating system has been upgraded to Windows 10 from Windows 7. The operating system belongs to the same OS family and only cosmetic changes were made.	Not significant This is a change to the operating system on which the unchanged software is running. Only cosmetic changes were made.
Software – cybersecurity	A security vulnerability is found in a device's software through routine cybersecurity monitoring. The software is modified to eliminate the vulnerability. No other changes are made. There is no further impact to the software or device.	Not significant The change to the software is to return it to its intended specifications. No new features are integrated and specification are unchanged. Risk analyses determined there is no negative impact to the software or device.
Software – MLMD licensed with a PCCP	Changes to the device that are included in the list of allowable changes in the licensed PCCP.	Not significant Not significant because changes are pre-authorized within the PCCP.

Device	Proposed change	Significant or not significant
Software – diagnostic ultrasound	A diagnostic ultrasound system has multiple available measurement parameters. Based on a marketing survey of current customers, 1 measurement parameter provided for informational purposes only (not used for diagnostics nor risk mitigation) is removed in a software update.	Not significant This change in specification is not related to the intended use or safety mitigation. No new risks are introduced.

Changes in materials for non *in vitro* diagnostic devices

Changes in materials include any changes in the material source, supplier, processing methods, type, formulation and chemical, physical or electromagnetic properties. Each material change should be assessed on its own and together to determine its impact on the safety and effectiveness of the device.

This section focuses on the impact of material changes on the device. For example:

- biological safety and biocompatibility of the device
- bonding or adhesion to adjacent materials
- mechanical or physical properties

In general, a change to materials of human or animal origin is considered significant. For more information, consult:

- Guidance on the regulation of medical devices manufactured from or incorporating viable or non-viable animal tissue or their derivative(s)

The impact of a material change on the safety or effectiveness of the device also depends on factors such as:

- the origin of the material
- if the material type, formulation, composition or processing has changed
- if the device is invasive or non-invasive
- the type and duration of the material's contact with body tissues or fluids

Changes to the materials of a medical device may also directly or indirectly impact several other aspects of the overall medical device or its function, for example:

- device specifications, resulting in altered mechanical performance
- device stability and shelf life
- a material change may require a change to labelling content
- sterilization process effectiveness, including interactions with sterilant

The impact of altering the materials of a Class II device that's compatible with a Class III or Class IV device, whether licensed together or separately, should also be considered. This change to the Class II device may impact the safety or effectiveness of the higher-risk device and require a licence amendment before the Class II material changes are made. For example, changes to the materials of a surgical stapler may have an impact on the safety or effectiveness of the compatible surgical staples.

Likewise, changes to other aspects of the design, manufacturing or storage and transportation should be assessed for potential intended or unintended impacts on the device or packaging materials. Examples of such changes include:

- changes in a manufacturing process or equipment could impact the properties of 1 or more device materials
- changes in storage conditions may influence material characteristics or stability of the device material or packaging materials

Change in the source or supplier of the material

A change in the source of a material refers to switching from 1 supplier or manufacturer of a raw material, component or substance used in the device to another.

In general, changes to the supplier or vendor are not considered significant when the change does not alter the material type, formulation, chemical composition or processing. This is regardless of whether the device comes into direct contact with a patient.

However, changes that affect the material type, formulation, chemical composition or processing are likely significant. This is especially the case when the material is implanted, has direct patient contact or is essential to the safety or effectiveness of the device.

Change in material processing

A change in material processing is to any modification in how a material used in a medical device is manufactured, treated or handled during production.

The impact of such a change should be assessed by comparing the modified material specifications against the original specifications. A material-related change that results in an alteration to the device specifications should also be evaluated as a design change.

When only the material specifications are affected and all other device specifications remain unchanged, the change is likely significant if it could reasonably be expected to impact the safety or effectiveness of the device.

Examples of material processing changes that may affect device safety or effectiveness include:

- changes to material extrusion equipment that could modify surface roughness
- adjustments to E-beam or gamma sterilization dosage that may alter the properties of a crosslinked polymer

Change in type of material

A change in the type of material refers to the substitution of one material for another that differs in chemical composition, biological origin, or physical properties. This is distinct from changes related to supplier or processing methods.

A change in the type of material is likely significant if the altered material may:

- have different biocompatibility characteristics
- change the performance or function characteristics of the device
- alter electromagnetic properties such as magnetic resonance imaging (MRI) compatibility or susceptibility to radiofrequency (RF) interference
- introduce new risks or change the device's benefit-risk profile
- affect the stability or durability of the device component
- affect the effectiveness or safety of the sterilization process or packaging system

Change in the formulation or chemical composition of the material

A change in the formulation and chemical composition is any change to the ingredients, ratios or chemical structure of a material used in the device. This includes:

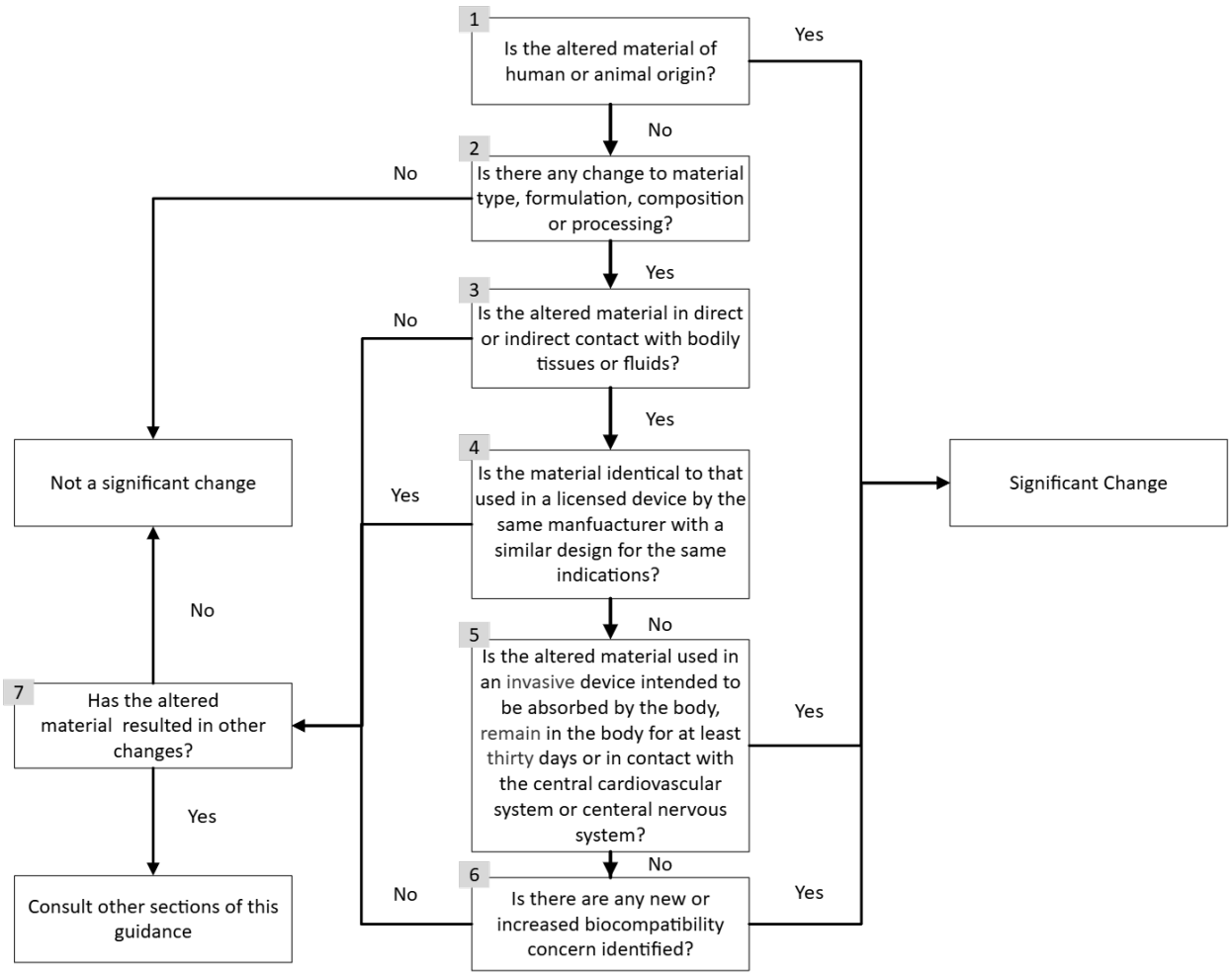
- substituting 1 chemical compound for another
- altering the concentration or proportion of components within a mixture
- adding or removing additives, stabilizers or fillers
- changing the polymerization method or cross-linking agents

A change in the formulation or chemical composition of the material is likely significant if the:

- altered material is in direct or indirect contact with body tissues or fluids
- change affects the biocompatibility of the device
- modifications alter the mechanical, chemical or thermal properties of the device
- change in material has the potential to modify the overall benefit-risk profile of the device

The following flowchart and explanation outline the assessment you must undertake to determine if your change is significant.

Figure 1: Flowchart outlining the decision-making process for changes in material for non-IVDD devices



Additional considerations

Changes to reuse or recycling processes or to storage conditions for raw materials intended for additive manufacturing such as 3D printing are likely significant if the properties or performance of the finished device are affected.

If the altered material will be in direct or indirect contact with body tissues or fluids, it is likely significant.

- Direct contact refers to physical contact between the material and body tissues or fluids.
- Indirect contact refers to a material through which a fluid or gas passes before the fluid or gas comes into physical contact with body tissues or fluids. In other words, the material itself does not physically contact body tissues or fluids.

For device safety, direct and indirect contact with body tissues or fluids should be assessed using the same considerations. Any change involving either type of contact may be significant, pending the full assessment.

If the material has neither direct nor indirect contact with body tissues or fluids, no further biological or biocompatibility considerations need to be assessed in terms of significant change.

If the altered material is in contact with body tissues or fluids, but the altered material is used in a Canadian-licensed device with a similar design for the same indications by the same manufacturer, the material change may not require an amendment. This is the case if:

- both devices are manufactured by the same process **and**
- for the same indication **and**
- the material interacts with the same adjacent materials in both devices

The licensed device must also have all of the following:

- same or greater risk classification
- same or higher risk nature of contact
    - for example, blood is considered worst-case or higher risk compared to intact skin
- same or longer duration of contact

Biocompatibility concerns reported in a post-market clinical follow-up or surveillance and part of the corrective action or mitigation includes a change to the materials would be considered a significant change.

A change is likely significant if there's a change made to materials used in an invasive device that's intended to:

- be absorbed by the body
- remain in the body for at least 30 days **or**
- be in contact with the central cardiovascular system or central nervous system

The material change is likely not considered significant if:

- it is a colourant change using an altered dye that complies with List 7 of the FDA's Colour Additive Status List **and**
- no other changes are introduced

If the device doesn't meet these conditions, then biocompatibility assessment should be performed. A material change that could introduce a new or increased biocompatibility concern is considered a significant change.

- A new biocompatibility concern refers to the scenario where a new type of biocompatibility testing is required.
- An increased biocompatibility concern refers to the scenario where the original biocompatibility testing for the device no longer applies.

For example, if a material change introduces a new leachable that needs to be tested:

- a new biocompatibility concern would result if the leachable is suspected to be genotoxic and no previous genotoxicity testing of the original device was conducted
- an increased biocompatibility concern would result if sensitization testing of the original device is no longer applicable due to sensitization potential of the leachable

A material change is likely not significant if it:

- does not introduce new or increased biocompatibility concerns **and**
- is not used in a device intended to be absorbed by the body **and**
- is not intended to be retained in the body for 30 days or more **and**
- is not intended to be in contact with the central cardiovascular or central nervous system **and**

- does not result in any other modifications to the device's design, specifications, performance or overall safety

Table 6: Examples of material changes for non-IVDDs

Device	Proposed change	Significant or not significant
Implantable port	Change to the supplier of 1 of the patient- contacting implantable components. The port is indicated to remain in the body for more than 30 days. The device specifications are the same, but the material suppliers' specifications are not.	Significant Differences in material supplied may impact quality of those materials, which may in turn impact safety or effectiveness of the device.
Dental composite	Change to the concentration of a dental composite component. The device performance specifications are the same. The device stays in the body for more than 30 days.	Significant This is a change in a design specification that may impact safety or effectiveness.
Dermal filler	Change to the crosslinking degree of hyaluronic acid used in a dermal filler. The formulation of the device is the same. The device is absorbed by and stays in the body for more than 30 days.	Significant This is a change in a design specification that may impact safety or effectiveness.

Device	Proposed change	Significant or not significant
Breast implant	Change to processing equipment that alters the specifications of the material used in a breast implant. The device stays in the body for more than 30 days.	Significant This is a change in a design specification, intentional or not, that may impact safety or effectiveness.
Oxygenator	Change to the membrane material used in the gas-exchange part of an oxygenator. The material has not been used in another licensed oxygenator. It's not in contact with body fluids for more than 30 days. However, there is an increased biocompatibility concern about this material.	Significant There is a potential new risk introduced that may impact the benefit-risk profile of the device.

Device	Proposed change	Significant or not significant
Hemodialysis system or console	Change to the material used in the pressure sensor of a hemodialysis system fluid path. The altered material is identical to a material used in a temperature sensor in another licensed hemodialysis system fluid path. Both hemodialysis systems are made by the same manufacturer with the same indications for use. They only differ in software features. There are no other changes.	Not significant The risks associated with the material have already been reviewed by Health Canada for an equivalent intended use and deemed acceptable Note: The comparator must have explicitly been identified to Health Canada and undergone pre-market review (new or amendment).
Neurovascular suture needle	Material used in a neurovascular suture needle changed from 304 stainless steel to 316 stainless steel. The same manufacturer has another neurovascular suture needle licensed in Canada that uses the same 316 stainless steel and has undergone successful pre-market review. The needle mechanical performance specifications are the same.	Not significant The risks associated with the material have already been reviewed by Health Canada for an equivalent intended use and deemed acceptable.

Device	Proposed change	Significant or not significant
Percutaneous transluminal angioplasty (PTA) balloon dilatation catheter	Ink used on the proximal marker of a PTA balloon dilatation catheter changed from white hot stamp ink to a black TP300 N50 ink. This ink is in contact with patients. The new ink has previously successfully undergone pre-market review in Canada for a device by the same manufacturer. This device has the same or equivalent nature of body contact and contact duration as defined by ISO 10993-1.	Not significant The risks associated with the material have already been reviewed by Health Canada for an equivalent intended use and deemed acceptable.
Cardiovascular stent delivery system	Change to the material of the handle of a cardiovascular stent. There is no change to the design of the handle and the handle does not come in contact with the patient.	Not significant Deemed unlikely to alter the benefit-risk profile of the device.

Device	Proposed change	Significant or not significant
Hip implant	Change to the supplier of titanium alloy used to manufacture the hip stem. The material continues to conform with ASTM F136.	Not significant The safety, effectiveness and quality of the material is supported by a Health Canada-recognized standard and there is no change to the device specifications.
Peripherally inserted central catheter (PICC)	Colourant change to the insertion hub of a PICC that is part of the fluid path for fluid administration or withdrawal from a patient. The colourant complies with the FDA List 7 Color additives exempt from certification (unless otherwise indicated) and permanently listed for use in medical devices.	Not significant Including colour additives on the FDA List 7 (exempt from certification) will be deemed non-significant for medical devices.

Device	Proposed change	Significant or not significant
Peripherally inserted central catheter (PICC)	Colourant change to 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 to be used for fluid administration or withdrawal from a patient. The colourant does not come in contact with body tissues or fluids directly or indirectly.	Not significant The colourant is used in the flush port of a PICC that has no contact with body tissues or fluids and there is no other change.

Changes in materials for *in vitro* diagnostic devices

There is a distinction between *in vitro* diagnostic devices (IVDDs) and other devices regarding material changes.

Material changes to an IVDD include those made to:

- critical components
    - such as antigens, antibodies, primers, conjugates
- other reagents
    - such as buffers
- materials that are in direct contact with device reagents
    - such as cassettes, solution bottles

A material change to a critical component of an IVDD is likely significant when the risk assessment identifies a potential impact on the safety or effectiveness of the device, such as:

- impact on a performance claim
- impact on the approved shelf-life or stability claim
- affects the operating principle of the device (for example, from immunofluorescence to ELISA)
- changes the operating principle and thus IVDD performance characteristics, including specificity or sensitivity
    - The impact of each change on the safety and effectiveness of the device should be considered.
- changes reaction components or materials such as calibration materials resulting in altered performance characteristics reflected in the labelling

Material changes to an IVDD may also lead to changes in the design, manufacturing process, equipment, control procedures or labelling, including stability claims. You should consult all relevant sections of this guidance to determine if your proposed change is significant.

Table 7: Examples of IVDD material changes

Device	Proposed change	Significant or not significant
IVDD test kit	Sodium azide added as a preservative to a reagent of the kit. This introduces a new hazard and requires that a warning be added to the labelling.	Significant This introduces a new hazard, impacting the safety profile of the device and requiring changes to the labelling.

Device	Proposed change	Significant or not significant
IVDD test kit	Glass reagent bottles replaced with plastic reagent bottles to address breakage issues, resulting in manufacturer specifications changing the container. A new stability study is required to establish stability of the reagent using the new container material.	Significant Stability of the reagents may be impacted.
IVDD test kit	Sample preparation changed to include a stabilizer. A risk assessment shows that adding a stabilizer may impact the assay's performance.	Significant Change in materials and component specification may impact performance of the device.
IVDD test kit	External positive control source material changed from human antibody to non-human antibody. The change requires a new stability study as the stability of the newly formulated control has not been established.	Significant Quality control measure is impacted by the material change, which may impact the stability of the device, the risk profile or labelling claim.

Device	Proposed change	Significant or not significant
IVDD test kit	Primary packaging changed from a less to a more water-permeable material (for example, highly impermeable foil to plastic). Risk assessment identifies a possible impact on the device stability claim.	Significant Quality control measure is impacted by the material change, which may impact the stability of the device, the risk profile or labelling claim.
IVDD test kit	Change to the sample extraction buffer pH is made to improve extraction efficiency. Based on risk assessment, no new risk has been introduced. Changes to extraction buffer pH only improved efficiency of the methodology. Product specifications were not changed. No changes to labelling were made.	Not significant There is no expected impact on safety based on risk assessment.

Device	Proposed change	Significant or not significant
IVDD test kit	Change in PBS buffer within a test kit due to a supplier change with no change to the manufacturer's specifications. Risk assessment and quality control testing do not identify an impact on safety or effectiveness of the device and no new stability studies are warranted.	Not significant As there is no change to acceptance specifications of supplied material, no new risk is introduced. Existing quality control measures are unchanged.
IVDD test kit	Change in the preservative of control material for which a risk assessment confirmed that the risk profile, performance characteristics and stability claims remain unchanged.	Not significant Risk assessment confirmed that the risk profile remains unchanged.

Changes to labelling

The labelling of a device contains important information about its safe and effective use. Some labelling changes are considered significant. Each labelling change should be assessed individually, as well as in the context of the cumulative impact of all labelling changes made over time.

Changes to labelling can include changes to:

- user manuals
- patient labelling
- electronic labelling
- instructions for use
- labels affixed on the device
- manufacturers marketing materials including websites intended for Canada
- any other documents that provide information related to the use of the device

Changes that trigger an update to the labelling should also be evaluated against all other relevant sections of this guidance. For example, labelling changes are often triggered by changes to:

- user requirements
- performance specifications or materials
- the design of the user interface

Labelling changes related to indications for use, intended use and clinical benefits

In general, changes to the intended use or indications for use are considered significant. The exception is if they are a subset of the intended use or indications for use. The revised subset of the statement must be based on the currently licensed intended use or indication for use that was previously reviewed under a medical device licence application. In this case, be sure to:

- still include the same text for the majority of the intended use or indications for use **and**

- remove previously approved text to create the subset of the intended use or indications for use

The following general principles apply:

- clarifying terminology that is clinically equivalent is less likely to result in a significant change
- generalizing or broadening claims is likely to constitute a significant change

The addition of a new patient subgroup to the indications or intended use is typically a significant change. This is especially true if the:

- subgroup may be considered higher risk or more vulnerable than the population previously identified
- change introduces usage of the device that is not widely accepted medical practice in Canada for that type of device

The following situations would also likely be considered a significant change:

- a limitation to the indications for use is introduced because of concerns associated with the safe or effective use of the device
    - note that a contraindication or a warning should also be added to the labelling in this case
- wording is modified to state or imply that new clinical evidence exists to support the claim beyond what was previously submitted and reviewed by Health Canada
    - involves new wording and new stated or implied claims
- the indications for use are modified to allow use only in cases where an explicit medical condition exists
    - requires clinical evidence to support the claim

Adding a patient subgroup may not be significant if the identified subgroup:

- is added for clarification
- is not considered higher risk or more vulnerable than the patient population identified in the previous indications or intended use **and**
- would have been clinically assumed within the indications for use for the licensed device

Example of a non-significant change involving a patient subgroup:

- A device previously indicated for people with heart failure is revised to indicate for adults with heart failure. Although this clarifies a specific patient subgroup, but does not introduce a vulnerable population, as adults would reasonably be assumed to be included in the general previous indication.

Examples of a significant change involving a patient subgroup:

- The change includes adding pediatric patients, the previous indications were general and did not refer to patient age. Pediatric use is not widely accepted medical practice in Canada for this type of device.
- The change includes adding patients with diabetes, expanding the indication beyond the previously general population and altering the benefit-risk considerations.

Reducing indications for use to a subset of the original population is often a non-significant change.

Example of a non-significant change involving a patient subgroup:

- A device indicated for patients who experienced a heart attack is revised to specify “adult” patients who experienced a heart attack. This is a clarification, does not introduce a higher-risk population and follows the widely accepted medical practice for the use of the device in Canada.

Other types of significant labelling changes

Examples of other significant changes to labelling include:

- changes that alter label content about when, where or by whom the device is used
- new claims associated with earlier interventions in the disease progression compared to current labelling claims for the licensed device
- new claims that may change the environment in which the device is used
    - such as a change from a hospital setting to an office or home setting
- new claims that alter who can use the device
    - such as changing from a health care practitioner to a technician, patient, caregiver or the public

Examples of changes to warnings, precautions or possible adverse events that may not be significant include:

- minor changes that clarify the existing wording of warnings and precautions
- relocating a warning or precaution when the same information is already included, labelled as a warning or precaution and presented identically elsewhere in the labelling
- adding a warning or precaution for health care professionals that reflects a well-established standard of practice in Canadian clinical settings for using the type of device
    - for example, “do not implant the device in patients with sepsis”

Examples of changes to warnings, precautions and possible adverse events that are significant include:

- adding or removing a contraindication
- removing a warning or precaution from the labelling
- adding a warning or precaution driven by new information related to a previously unidentified or identified hazard affecting safety or effectiveness of the device
    - Information may arise from incident trending, user feedback, scientific literature or national registry data regardless of hazard type.
    - For more information on definitions of precautions and warnings, refer to Guidance for the labelling of medical devices, not including in vitro diagnostic devices - Appendices for the labelling of soft, decorative, contact lenses and menstrual tampons.
- removing possible adverse events when they formed part of the device’s risk mitigation plan previously reviewed or required by Health Canada
- adding a new possible adverse event due a newly identified safety concern

Adding a clinical benefit to the labelling may introduce new claims or expand existing claims made in the indications for use. In most cases, this constitutes a significant change.

Examples of a significant change involving the addition of a claim include:

- new claims (explicit or implied) related to safety or effectiveness that require supporting data
- new representation of uncertainties about performance that require supporting data

Example of a non-significant change involving the addition of a claim include:

- adding a clinical benefit where the statements are fully within the scope of the licenced indications for use and the supportive information already appears in the existing licensed labelling

New labelling, including for marketing purposes, that targets new populations may not be significant. The change must stay within the scope of the claims that Health Canada reviewed for the licensed device. Any labelling that goes beyond those claims may be considered significant.

Examples of a non-significant change involving a change in population:

- new labelling that does not introduce new claims or statements about device safety, effectiveness, uncertainty or therapeutic mechanisms, beyond the scope of licensed indications for use, intended use or the general description of use included in the labelling which underwent pre-market review for the licensed device

For IVDDs, examples of changes that are likely significant include:

- identifying a new subpopulation for which clinical data were not previously been provided
    - This change would **not** be significant if clinical data for the subpopulation were already submitted and reviewed.
- adding or removing limitations that do not appear in the intended use but appear elsewhere in the package insert
    - This change is not significant if it does not impact the correct use, performance or interpretation of correct results, supported by usability assessment or clinical experience.
- removing a warning or a precaution
    - Adding a warning or precaution is likely not a significant change, unless it also impacts the intended use.

Changes in labelling concerning reprocessing, sterilizing, cleaning or disinfection

Medical devices that are reprocessed, sterilized, cleaned or disinfected by the end user must include manufacturer-validated instructions for the cleaning, disinfection and sterilization process.

For more information, consult:

- Information to be provided by manufacturers for the reprocessing and sterilization of reusable medical devices

Changes to the recommended reprocessing, sterilizing, cleaning or disinfecting method of a product compared to the previously submitted and reviewed method for a licensed Class III or IV device may be considered significant. Removing a recommended reprocessing method or product from the labelling or package insert may not be a significant change if alternate, validated options licensed in Canada are still included in the labelling.

Labelling changes concerning other regulatory jurisdictions

For information on adding a clinical benefit to labelling, refer to the subsection on changes concerning indications for use, intended use and clinical benefits.

Modifications to the labelling made solely to include additional languages (other than French or English) required in other regulatory jurisdictions is not considered a significant change.

Changes related to references in the labelling are significant if they:

- add or modify wording related to references for articles that relate specifically to off-label use of the medical device compared to the currently licensed Canadian labelling
- add references related to off-label usage compared to Canadian-licensed claims
- add or imply new claims for the device compared to those that underwent successful premarket review to obtain a medical device licence for the Canadian market

When it comes to references, the following are not considered significant changes:

- introducing new references to data from third-party databases required for other regulatory approvals, where the database content is clearly intended for non-Canadian audiences
- including references to publicly available information, such as journal articles, provided these do not introduce or imply new claims or promote off-label use relative to Canadian-licensed labelling

It is not considered a significant change to remove references to obsolete devices from the instructions for use when those devices are no longer available for sale in Canada.

Labelling changes concerning the useful life of a product or shelf-life

The benefit-risk profile, safety or effectiveness of a medical device may be impacted by the date of manufacturing or packaging. Evidence supporting compliance with the regulation*s* is based on both the recommended or predicted duration of safe device use and the duration of protection provided by the product's packaging.

Examples of a significant change include:

- introducing a new statement about the projected useful life of a device that specifies a timeframe (for example, 90% freedom from device failure at 3 years) that was not included in the currently licensed labelling
- making claims for shelf-life extension when the:
  - protocols and methods used to determine shelf-life have changed or were not previously reviewed as part of a pre-market application
  - results or acceptance criteria differ significantly from data previously reviewed by Health Canada
- reducing the shelf-life when a change has affected the safety or effectiveness of the device or when other considerations have changed the benefit-risk profile

Examples of a non-significant change include:

- adding broad statements without specific claims, such as adding a statement that the device may need to be replaced in the future, without adding a defined useful life claim
- making shelf-life extension claims, including for IVDDs, if the new claims were validated, using the same protocols, methods and acceptance criteria previously reviewed and accepted by Health Canada when the licence was issued
    - If any of the parameters change during the validation of the shelf-life extensions, the change becomes significant.

Labelling changes to include unlicensed devices

It is illegal to advertise or market for sale an unlicensed device in Canada.

It may be acceptable to include model numbers or device listings within the labelling provided no detailed content or instructions related to the unlicensed devices are included.

Changes to international labelling made solely for the purpose of listing devices not intended for sale or no longer for sale in Canada may be considered non-significant if all of the following conditions are met:

- the labelling does not include promotional language or otherwise advertise the unlicensed device for sale **and**
- there is no claimed interoperability between the unlicensed device and your device that is unsubstantiated **and**
- the indication for use or intended use of your device does not depend on the unlicensed device **and**
- the reference to the unlicensed device is not misleading to the Canadian user and can be disregarded without affecting the safety and effectiveness of the licensed device **and**
- use of the unlicensed device is not required for your device to meet the requirements of sections 10 to 20 of the regulations

Labelling changes to include compatible devices

“Compatibility” refers to the ability of a device, when used with another device or devices, to achieve the intended overall clinical purpose without the user having to modify or adapt any part of the combined devices.

Changing the labelling of a Class II, III or IV device to claim compatibility with a separately licensed Class III or IV device is often considered a significant change for the Class III or IV licence. This applies to:

- adding a compatibility claim to both devices, where both devices are from the same manufacturer
- adding a compatibility claim to a Class II, III or IV device, where the manufacturer of the second device is different
    - for example, adding a compatibility claim between a polyethylene liner and a separately licensed femoral head

To illustrate:

- Licence 1 has Device A, with a list of compatible devices that includes Device B
- Licence 2 has Device B, which is currently intended to be used with Device A
- Licence 3 has Device C, which currently has no compatibility claim

Adding a compatibility claim to Licence 1 (Device A) may not be significant if:

- Device C is equivalent to Device B, which is currently listed as compatible devices **and**
- adding the compatibility claim to Device A or C does not introduce a significant change under any other section of this guidance **and**
- Device C is not significantly different from Device B based on all relevant criteria in this guidance, and is manufactured by the same manufacturer as Device B

However, adding Device C as a compatible device to Licence 1 is likely a significant change if the:

- manufacturer of Device C and B are different **or**
- addition of compatibility between Device A and C impacts the indications for use of either device

If you have a compatibility claim involving a device from a different manufacturer, you should monitor for changes to that device that could invalidate a compatibility claim with your device. A significant change made by the third-party manufacturer that affects safety or effectiveness of the paired use would constitute a significant change for your device.

Removing an approved compatibility claim may be considered a significant change if the:

- removal is due to concerns with the safe or effective use of the assembled compatible devices **and**
- change impacts how the devices interact with each other or how the system will perform

For changes to compatibility claims involving a compatible Class II device, refer to the section on Class III or IV amendments concerning separate compatible Class II devices.

Labelling changes concerning magnetic resonance

In general, any change to the magnetic resonance (MR) safety claim of an licensed medical device, including changes to the scan conditions under which an MR scan may be safely performed, is considered a significant change.

Examples of non-significant changes:

- The device is implantable and composed of non-magnetic materials (for example, a polymer implant), and an MR-safe claim is being explicitly added to the labelling.
- MR conditional claims are reduced to a subset of previously licensed MR conditions.

Table 8: Examples of labelling changes

Device	Proposed change	Significant or not significant
All devices	Removing the statement "not for pediatric use" from the contraindications section or another section of the labelling. **or** Removing a contraindication against lip augmentation for a dermal filler from the patient flier and Canadian website. **or** Removing the contraindication against the use of a dental implant in patients who smoke from the package insert.	Significant The benefit-risk profile is impacted by this change as it alters the patient population for which safety and effectiveness may or may not have been supported previously.
Dermal filler	Deleting potential adverse events, such as granuloma formation, from the labelling.	Significant The regulations require the manufacturer to provide information relative to risks that cannot be eliminated. This change may impact the risk profile or mitigation measures in place for the device.

Device	Proposed change	Significant or not significant
Stent graft	Modifying the indications for use to exclude femoral implantation, but this was previously explicitly indicated. This change is implemented due to safety concerns identified in post-market use.	Significant Although the change narrows the claims, the reason for the change is safety-related.
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 being added to 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. The labelling is being updated to detail the new mode and list compatible probes.	Significant The additional mode would be a significant design change. The change in labelling also expands the indications for use beyond the scope of the currently licensed indications for use and claims new compatibility with other licensed devices.

Device	Proposed change	Significant or not significant
Radiofrequency probe	The radiofrequency probe is indicated for ablating nervous tissue (used peripherally). Modifying indications for use so that the probe may now be used in the central nervous system (for example, brain).	Significant Changing the indications for use beyond the scope of the currently licensed indications for use.
Ventricular assist device	Modifying indications for use from an adult population to a population with a mass greater than 20 kg.	Significant Adding a new patient population subgroup that is outside the scope of the current claims. The new population is also considered more vulnerable than the original intended population.
Total knee replacement	Adding clinical benefit to state that a total knee replacement has 80% reliability at 15 years.	Significant Adding new performance uncertainty claims and a new projected useful life statement with a specific timeframe.

Device	Proposed change	Significant or not significant
Blood pressure monitor	Labelling and patient pamphlet have been revised to recommend use only in patients who have hypertension above 150mm Hg. This reduces the patient population in the Canadian-licensed labelling to a subset. This is based on empirical data in the literature showing highest performance in this subpopulation.	Significant The change is based on new safety or effectiveness information.
Peripheral stent	The indications for use list multiple uses explicitly, but 2 are being removed to align with international labelling. Another regulatory jurisdiction requested the 2 claims to be removed due to lack of use in their jurisdiction. The change is not based on safety concerns.	Significant The change narrows the intended population to one that was not previously explicitly stated. This is not considered a clarification.

Device	Proposed change	Significant or not significant
Patient monitor	Labelling for a patient monitor is being modified to reference a licensed third-party diagnostic probe. A similar probe is not currently claimed to be compatible with the patient monitor. The manufacturer of the patient monitor has access to the safety, effectiveness and compatibility evidence for the diagnostic probe.	Significant This is a design change that may significantly affect the safety and effectiveness of the patient monitor. The labelling change is outside the previously licensed scope (expanded or modified indications).
All devices	Labelling change to include additional languages, other than French or English, required in other regulatory jurisdictions.	Not significant The change does not impact the labelling claims, mitigations and device details are unchanged for labelling in both Canadian official languages.

Device	Proposed change	Significant or not significant
Knee implant	The marketing materials and website have been updated to state that knee implants have a finite life and future revisions or replacement may be required. No specific timelines are added as part of the labelling change. Adding the following to the physician labelling: “The projected useful life of this depends on use and patient characteristics”. This statement is added to previously existing and Health Canada reviewed statement that the device’s projected life is 20 years.	Not significant Adding a broad statement without a claim.
Structural heart defect device (PFO closure)	Modifying indications for use to indicate adults, to clarify it is to be used in adults older than 21 years of age. Change aligns with U.S. definition of adult and is not due to safety concerns.	Not significant Clarifying the intended population subgroup.

Class III and IV amendment requirements due to changes to compatible Class II devices

“Compatibility” refers to the ability of a device, when used with 1 or more other devices, to achieve the intended overall clinical purpose without the user needing to modify or adapt any part of the combined devices.

An important requirement in demonstrating the safety and effectiveness of medical devices that are to be used together is compliance with section 18 of the regulations. Under section 18, a medical device intended to be used together with other medical devices must:

- be compatible with each medical device it is intended to be used with **and**
- not adversely affect the performance of the medical devices used together

Refer to the following notice for the situation when the devices are licensed separately:

- Licensing requirements for inter-dependent medical devices

As noted in the section on general principles, Class II amendments are not within the scope of this guidance document.

However, changes made to a Class II device that is compatible with a Class III or IV device may alter the safety and effectiveness of the Class III or IV device. This is the case even if the design of the Class III or IV device remains unchanged.

Such changes may represent a significant change for the Class III or IV licence and could therefore require a Class III or IV amendment before the modified Class II device can be marketed.

Some devices are compatible with multiple devices. If changes are made to 1 or more of the compatible devices, you must ensure that the combination of medical devices continues to meet the requirements of section 18 of the regulations. Note that under item (d) of the significant change definition, new or extended uses resulting from these modifications are considered changes to the intended use.

This section applies to the following 2 scenarios:

1. The labelling of a Class III or Class IV device is being changed to indicate compatibility with a new or licensed Class II device, even if the formal “intended use and/or indications for use” statement of the Class III or IV is unchanged.
2. A change is being made to a licensed Class II device that is already indicated as compatible with a licensed Class III or IV device.

To evaluate whether either of these 2 scenarios are significant changes for the Class III or IV licence, you must assess if they may affect the safety or effectiveness of the Class III or IV device. Consider the following factors:

- critical nature of the Class II device
    - the more critical the Class II device is to overall system function (including safety or effectiveness), the more likely the compatibility change could affect the safety or effectiveness of the Class III or IV device
    - the following changes would be considered significant:
        - indicating the device can perform a task or treat a condition for a different duration of time
        - the Class II has or introduces new clinical indications or intended uses beyond or more specific to those of the licensed Class III or IV claims
        - the Class II has a different target patient population
        - changes that necessitate new clinical studies or usability studies
        - changes to the therapy delivered
        - introducing a new operating workflow or user interface
- differences in key design specifications between the Class II device previously indicated as compatible and the new or modified Class II device

You should identify and analyze how such differences could impact safety and effectiveness of the overall system. This includes assessing whether the change may affect factors such as compatibility, performance and risk mitigations.

An amendment for both the Class II licences and the Class III or Class IV licences would be required if a change is deemed significant for compatible devices on different authorizations.

Table 9: Examples of changes to compatible devices

Device	Proposed change	Significant or not significant
Class II swab used to collect endocervical specimens	The validation of the swab for use with a specific Class III Chlamydia test was reviewed as part of the application for that test. A change is made to the specifications of the swab (for example, in material or design).	Significant The change to the swab could impact the safety or performance of the test.
Class II delivery catheter indicated for use in the delivery of a Class IV cardiac implant	A Class IV cardiac implant is licensed as compatible with a Class II delivery catheter. In this example, the Class II device's labelling specifies the licensed access routes, but the Class IV device's labelling does not. Introducing a design change to the Class II delivery catheter system allows for a different access route than the one licensed in the initial application. New clinical testing was required to support the safety and effectiveness of the overall system.	Significant The change to the delivery catheter impacts the clinical performance of the devices when they are used together, including a potential increase in risk and complications in delivering the cardiac implant.

Device	Proposed change	Significant or not significant
Class II insulin infusion set	Adding a new Class II insulin infusion set to a Class III or IV programmable insulin pump's list of compatible infusion sets. The new infusion set is indicated for a longer wear period than the infusion sets that are previously indicated as compatible with the pump and longer than stated in the pump labelling. The longer wear period necessitated new testing activities to support the safety and effectiveness of the therapy delivered by the overall system.	Significant The longer wear period could impact the clinical performance of the devices when they are used together.
Change in reprocessing of a Class III or IV device using a Class II disinfectant	A licensed Class III or IV device is labelled for use with a Class II disinfecting device. The specifications of the Class II disinfecting device are changed due to a change in supplier.	Significant The change to the specifications of the disinfecting device could impact the performance or safety of the Class III or IV device.

Device	Proposed change	Significant or not significant
Class II surgical stapler	The specifications of the stapler have been changed to address recommendations for end users. This includes the portion that houses the staple reloads, which are licensed separately on a Class III licence.	Significant The change to the stapler could impact the performance of the Class III staple reloads.
Class II sound processor	(Change 1) The software Alpha App is a key application for a manufacturer's sound processors. It is licensed separately as a Class II device. This software application is compatible with several Class III cochlear implants as well as Class II hearing aids by the same manufacturer. The software is updated to improve the performance of the implanted Class III device component.	Change 1 Significant The change in software impacts the safety or effectiveness of the Class III or IV device.
	(Change 2) A change is implemented to the same software to fix a configuration error related only to interaction with compatible hearing aids. There is no change to the	Change 2 Not significant The change does not impact the compatible

Device	Proposed change	Significant or not significant
	code specifically interacting with the cochlear implants or their processors.	Class III or IV licensed devices.
Class II administration set	Adding a new Class II administration set to a Class III programmable infusion pump's list of compatible administration sets. Following an engineering analysis and risk assessment, the manufacturer determined that the design parameters of the new administration set fall within the design parameters of the administration sets. These are already indicated as compatible with the pump (for example, tubing dimensions and material, number and characteristics of integrated components, manufacturing processes, including sterilization). Verification testing was done to	Not significant The design parameters of the new administration set fall within the design parameters of administration sets previously licensed as compatible with the pump. As well, the same testing activities were reviewed in a previous licence application and the testing did not produce any unexpected results.

Device	Proposed change	Significant or not significant
	confirm that the pump performs as expected with the new administration set using the same testing activities that were reviewed in a previous Class III pre-market application. The testing did not produce any unexpected results. There are no changes to the intended use or indications for use compared to the licensed administration sets.	

Changes to diagnostic ultrasound systems

Health Canada recognizes that there are a number of licensed diagnostic ultrasound systems that have a well-established safety profile in Canada and in other regulatory jurisdictions.

A change made to a diagnostic ultrasound system will not be considered significant **if all** of the following apply:

- intended use or indications for use remains unchanged and the modifications **do not** introduce intracardiac or intravascular imaging through catheter-based transducers
- modifications **do not** introduce sterile use or sterilization where previously not indicated and **do not** affect previously indicated sterile use
- modes of operation for the modified device are well established:
  - well established modes include A-mode, B-mode, M-mode, Doppler (CW, Color, PW, Power, Combination), speckle-tracking, tissue harmonic imaging and combination
  - **not well-established** modes include shear wave elastography, acoustic attenuation mapping, transmission-based imaging and sound speed measurement
- modifications **do not** lead to acoustic outputs that exceed the recommended maximum acoustic output levels
  - refer to Device licence applications for diagnostic ultrasound systems and transducers: Notice to industry
  - $I_{SPTA.3}$
    - < 720 mW/cm^2 (most applications)
    - <430 mW/cm^2 (cardiac)
    - <17 mW/cm^2 (ophthalmic)
  - $I_{SPPA.3}$
    - < 190 W/cm^2 (for most applications)
    - <28 W/cm^2 (ophthalmic)
  - MI
    - < 1.9 (most applications)
    - <0.23 (for ophthalmic)
- modifications **do not** result in any ultrasound interrogation parameters outside each of the following ranges:
  - centre frequency: 1 to 20 MHz

  - rarefactional pressure: 0 to 7 MPa peak
  - pulse length: 1 to 100 cycles (except for CW Doppler)
  - pulse repetition frequency: 100 to 20,000 Hz
- modifications **do not** use novel mechanical or thermal effects for imaging or measurements
- modifications **do not** introduce diagnostic or diagnostic support functions developed by the same manufacturer that represent previously unlicensed capabilities
- measurements and analyses are clearly described and the user can adjust the following associated control parameters
  - image processing should be reversible or the original image should be available to the user
  - user is able to edit or adjust user-activated post-processing applications used for measurements (for example, segmentation and registration)
  - where applicable, user should be able to edit assumed values, parameters or thresholds in equations or algorithms used to generate additional outputs based on measurements of anatomical dimensions, tissue velocity or pixel intensity
  - labelling provides complete information about the processing or compression algorithms used by the device, when appropriate
- integrated transducer element check is performed each time a transducer is connected to the main system or activated to help ensure appropriate transducer performance
  - for example, an impedance check of each element may provide a preliminary evaluation of the element integrity and function
- transducer surface temperature falls within the requirements of IEC 60601-2-37
- if the device is for endocavity use, labelling includes clear, manufacturer-validated cleaning and disinfecting instructions using products licensed for sale in Canada and identifies appropriate probe covers

Table 10: Examples of changes tor diagnostic ultrasound systems

Device	Proposed change	Significant or not significant
Diagnostic ultrasound system	A software feature that uses shear-wave elastography to measure liver stiffness is being added.	Significant Shear-wave elastography uses novel mechanism for measurements.
Diagnostic ultrasound system	M-mode imaging is being added to the modes of operation of the device.	Not significant M-mode is a well-established imaging mode.
Diagnostic ultrasound system	A new transducer with the same indications for use as already licensed for the system. The acoustic output and interrogation parameters are within the defined limits.	Not significant Indications, acoustic output and ultrasound parameters are within the range of the system's current values and accepted limits.

Process and procedures

Introduction

You may still have questions even after you review this and other relevant guidance documents. Contact the Medical Device Directorate by email clearly stating “Significant change guidance request” in the subject line along with the related licence numbers. Your email should:

- include your assessment and current interpretation of your proposed change using this guidance
- provide specific areas of the proposed change that are not addressed by the guidance document
- include a list of all additional guidance documents consulted as part of your assessment

Send the email to meddevices-instrumentsmed@hc-sc.gc.ca.

Significant changes: Amendment application

For submitting an amendment application to medical device licences, you must use the application form specific to the device class. For the application forms refer to:

- Medical device application and report forms

You must also submit the supporting pre-market review documentation and evidence applicable to device’s risk classification. Note that identical changes made to Class III and IV devices may require different review components. All the review components must include information and documentation that is relevant to the proposed change.

For more information, consult:

- Guidance on how to complete the application for a new medical device licence

Health Canada will process your application in accordance with the following guidance document:

- Management of applications for medical device licences

Minor change

the new facility must be covered under your quality management system certification where:

- the manufacturer's name and address on the device labelling remain the same, but a new manufacturing facility (that is not a supplier or contract manufacturer) is added.

For medical device licences under Part 1, you must also submit an amended Company Template (CO) xml to make changes to existing device licences:

- Regulatory enrolment process web forms

Download and fill out the application attestation form to confirm that the manufacturing specifications are the same at the new facility. If you can make this declaration, we may amend your licence without needing additional safety and effectiveness data.

Non-significant changes

All non-significant changes that do not require a minor amendment, including changes to labelling, must be documented within the quality management system. After consulting this guidance, if the changes are not deemed significant, you must still report changes related to information or documents originally submitted with your medical device application to Health Canada. This is done at the time of annual renewal.

Recall

You are required to assess changes arising because of a recall to determine if they may constitute a significant change. Examples include changes to labelling, device design or design specifications. When submitting an amendment related to a recall, clearly indicate in your amendment application that it is related to a recall. This should not delay notifying customers of the recall and providing temporary measures to mitigate the risk associated with the recall.

For more information on what constitutes a recall and the recall process, consult:

- Guide to recall of medical devices (GUI-0054)

If you need additional guidance on whether a corrective action resulting from a recall requires an amendment to the licence, contact the Medical Devices Directorate by email at meddevices-instrumentsmed@hc-sc.gc.ca.

Abbreviations and definitions

Abbreviations

AI: artificial intelligence

AQL: acceptance quality limit

ASTM: American Society for Testing and Materials

CW: continuous wave

EO: ethylene oxide

IEC: International Electrotechnical Commission

ISO: International Organization for Standardization

IV: intravenous

IVDD/IVD: *in vitro* diagnostic device/*in vitro* diagnostic

MDR: Medical Device Regulations

ML: machine learning

MLMD: machine learning medical device

MR: magnetic resonance

OS: operating system

PCCP: predetermined change control plan

PICC: peripherally inserted central catheter

PTA: percutaneous transluminal angioplasty

PW: pulsed wave

Definitions

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

Control mechanism: The means by which the action of a device is directed or the output of a device is regulated.

Compatibility: The ability of a device, when used with 1 or more other devices, to achieve the intended overall clinical purpose without requiring the user to modify or adapt any part of the combined devices.

Design specifications: A set of device characteristics that clearly state the technical and performance criteria that a medical device meets. They must be measurable or verifiable. For example, the design specifications of a medical device can describe a device's:

- properties, such as dimensions, weight, mass, form, configuration or materials
- performance (or functional) characteristics, such as accuracy, strength, force, flexibility or energy source and output level

Facility: A site that's involved in the manufacture or design and manufacture of a medical device.

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

Precautions: Information that alerts the user to exercise special care for the safe and effective use of the device.

Recall: For a medical device that has been sold, 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 may:

- be hazardous to health
- fail to conform to any claim made by the manufacturer or importer about its effectiveness, benefits, performance characteristics or safety or
- not meet the requirements of the Food and Drugs Act or the Medical Devices Regulations

(MDR)

Significant change 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:

- manufacturing process, facility or equipment
- 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
- design of the device, including its performance characteristics, principles of operation, specifications of materials, energy source, software or accessories
- intended use of the device, including any new or extended use, any addition or deletion of a contraindication for the device and any change to the period used to establish its expiry date

(MDR)

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

(MDR)

Validation: Confirmation by examination and the provision of objective evidence that the requirements for a specific intended use have been fulfilled, as set out in the definition validation in section 2.18 of International Organization for Standardization standard ISO 8402:1994, Quality management and quality assurance.

(MDR)

Verification: Confirmation through provision of objective evidence that specified requirements (for example, comparing a new design specification with a similar proven design) have been fulfilled. Verification ensures a device performs as intended.

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.