Global Harmonization Working Party

Towards Medical Device Harmonization

PROPOSED FINAL DOCUMENT

Title:	Categorisation of Changes to a Registered Medical Device
Authoring Group:	Work Group 1, Pre-market: General MD Work Group 2, Pre-market: IVDD Work Group 3, Pre-market: Software as a MD
Date:	14 Feb 2023

Dr. Wen-Wei Tsai
Chair, Work Group 2
Dr. Se-Il Park
Chair, Work Group 1
Dr. Abdullatif S. AlWatban
Chair, Work Group 3

Acknowledgements

This Guidance document was led by Work Group 2 and drafted by Dr. Adelheid Schneider and Ms. Judy Cheung and with subsequent contributions from Work Group 1: Ms. Minghua Chen, Ms. Yon Ju Kang, Ms. Kate Hyeong Joo Kim, Ms. Victoria Qu, Mr. Edward Woo; Work Group 2: Dr. Christopher Chan, Mr. Daniel Chang, Ms. Karinis Chu, Ms. Sandra Chu, Mr. Duc Duong, Mr. Augusto Bencke Geyer, Mr. Henry Hou, Ms. Sheryl Hsiao, Mrs. Nutchnat Kitiwouranon, Ms. Pauline Law, Mr. Albert Poon, Ms. Shelley Tang, Ms. Tzu Ling Tseng, Dr. Veronica Wong, and Work Group 3: Mr. Duc Duong, Mr. Kelvin Koh and Mr. Tony Yip and Helena Ardura-Garcia of WHO, which we would like to greatly acknowledge.

Table of Contents

Preface

This document is produced by the Global Harmonization Working Party, based on change management guidances worldwide. The document is intended to provide non-binding guidance for use in the regulatory system of medical devices, including in vitro diagnostic (IVD) medical devices and software as medical device, and has been subject to consultation throughout its development.

1.0 Introduction

The objective of the Global Harmonization Working Party (GHWP) is to encourage convergence at the worldwide level in the evolution of regulatory systems of medical devices, including in vitro diagnostic (IVD) medical devices and software as a medical device in order to protect the public health by those regulatory means considered the most suitable.

This document has been developed to encourage and support global convergence of regulatory systems. It is intended for use by Regulatory Authorities (RAs), Conformity Assessment Bodies (CABs) and industry, and will provide benefits in establishing, in a consistent way, an economic and effective approach to the control of medical devices in the interest of public health. It seeks to strike a balance between the responsibilities of RAs to safeguard the health of their citizens and their obligations to avoid placing unnecessary burdens upon the industry.

During the life-cycle of a medical device, changes may take place from time to time. Changes made to a registered medical device must be linked to the principles of safety and/or performance (Essential Principles) and the ability of a risk based regulatory system to control the risk of the medical device placed in the market.

To ensure continued safety and/or performance of the medical device, a manufacturer must assess the effect of the change on the patient, practitioner and/or user of the medical device, and decide whether the change is expected to affect the safety and/or performance of the medical device.

According to the nature of the change, the RA will determine whether evidence of safety and/or performance has been appropriately collected and reviewed by the manufacturer based on the report made by the manufacturer.

Working Group 1, 2 and 3 of the GHWP have prepared this guidance document. Comments or questions should be directed to the Chair of GHWP Work Group 2 whose contact details may be found on the GHWP web page (http://www.ghwp.info/).

Note: The term “Registered medical device” refers to a medical device that can be legally marketed in the relevant jurisdiction.

2.0 Rationale, Purpose and Scope

2.1 Rationale

Consistent worldwide requirements for on categorisation of changes to medical devices would offer significant benefits to the manufacturer, user, patients and RAs. Eliminating or reducing differences between jurisdictions decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments.

2.2 Purpose

This document provides assistance to RAs and manufacturers in categorising and managing changes during the life cycle of medical devices. The document provides guidance on types of changes, principles of change categorisation, and what should be done by the manufacturer in relation to each type of change to its registered medical device. For minor changes, reference should be made into AHWP/WG1/F002:2016 Guidance for Minor Change Reporting, whereby the reportability depends on the jurisdiction.

2.3 Scope

This document applies to all products that fall within the definitions of Medical Device, In Vitro Diagnostic (IVD) Medical Device and software as Medical Device that appear within the GHWP document *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*.

3.0 References

AHWP/WG2-WG1/F001:2016 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*.

AHWP/WG1a/F002:2013 (now restructured to WG2) *Essential Principles of Safety and Performance of IVD Medical Devices.*

AHWP/WG3/F001:2015 Guidance Document on Medical Device Software - Qualification and Classification

Australia: Substantial changes affecting a TGA conformity assessment certificate and Transfers of certificate: Guidelines for notifying the TGA, v1.0, Jun-2017

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

Korea: Case examples of Medical Electrical Equipment with significant changes, 2018

Korea: Guideline for Change Management of IVD Medical Device (2019 Mar 5th version)

Malaysia: MDA/GD/0020 - Change Notification for Registered Medical Device

Singapore: GN-21 - Guidance on Change Notification on Registered Medical Devices

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

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

US: Guidance for Industry and FDA Staff – Modifications to Devices Subject to Premarket Approval (PMA) – The PMA Supplement Decision-Making Process – December 11, 2008

WHO: Reportable Changes to a WHO Prequalified in vitro diagnostic Medical Device, 2016

WHO: Reportable Changes to a WHO Prequalified Male Circumcision Device, 2019

Japan: PMDA document (PSEHB/MDED Notification No. 1020-1) - Handling of procedures for minor changes made in association with partial changes of medical device programs – October 20, 2017

US: Guidance for Industry and FDA Staff – Deciding When to Submit a 510(k) for a Software Change to an Existing Device – October 25, 2017

Korea: Guidance for Review and Approval of Artificial Intelligence-Enabled Medical Devices, May-2022

4.0 Definitions

Medical Device

The term is as defined in AHWP/WG2-WG1/F001:2016 “Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’

IVD Medical Device

The term is as defined in AHWP/WG2-WG1/F001:2016 “Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’”

Manufacturer

Manufacturer: For the purpose of this document, the term "manufacturer" must be understood to include the manufacturer, its authorized representative or any other person who is responsible for placing the device on the market.

Non-significant change[1]
A change that will not affect safety and/or performance of the medical device.

Quality Control (QC)
It is part of quality management focused on fulfilling quality requirements. (ISO 9000)

Quality Management System (QMS)

For the purpose of this guidance document, the term means the regulatory compliance and certification to ISO 13485 or its equivalent.

Regulatory Authority

1 The terms non-significant change and minor change are used in different jurisdictions but generally they can be used interchangeably.

It is a government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements. (AHWP/WG1a-WG7/PD007)

Risk Management is a systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk (ISO 14971:2007 Medical devices -- Application of risk management to medical devices)

Significant change[2] means a change that could reasonably be expected to affect the safety and/or performance of a medical device.

5.0 General Principles

To ensure continued safety and/or performance of the medical device, the manufacturer has to assess the impact of the change on the patient, practitioner and/or user of the medical device, and decide whether the change is expected to affect the safety and/or performance of the medical device. The following sections give guidelines on change categorisation and provide examples.

5.1 Assessment of Changes: General Principles

Changes to a registered medical device are categorised as significant (or major in some jurisdictions) and non-significant (or minor) change according to the effect on the safety and/or performance of the medical device.

A **significant change** (refer to definition of "significant change") means a change that could affect the safety and/or performance of a medical device.

A significant change typically may:

- Result in risks to the patient not previously identified
- Increase the probability of existing hazards occurring
- Alter the presentation of existing or new risks to the user (this can involve labelling changes or new indications for use)

A **non-significant change** is any modification that does not affect safety and/or performance of a medical device, which obtained a marketing authorization.

5.2 Reporting of Changes

According to the nature of the change, it is the RA that determines whether evidence of safety and/or performance has been appropriately collected and reviewed based on the reporting procedure made by the manufacturer[3].

2 The terms significant change and major change are used in different jurisdictions but generally they can be used interchangeably

3 In some jurisdictions, all changes whether significant or non-significant may need to be reported. In this case refer to the Guidance for Minor Change Reporting AHWP/WG1/F002:2016

Changes could be categorised either as significant or non-significant.

"Significant changes" are normally reported to the RA with supporting documentation to show the device is still safe and performing as intended.

"Non-Significant changes" are not normally reported to the RA, however the assessment and supporting documentation to show the device is still safe and performing as intended has to be reflected in the QMS system.

5.3 Tools to assess changes and the way of reporting

The following section presents flowcharts to assist manufacturers when assessing whether a change is considered to be a "significant change" which may need to be reported to the RA.

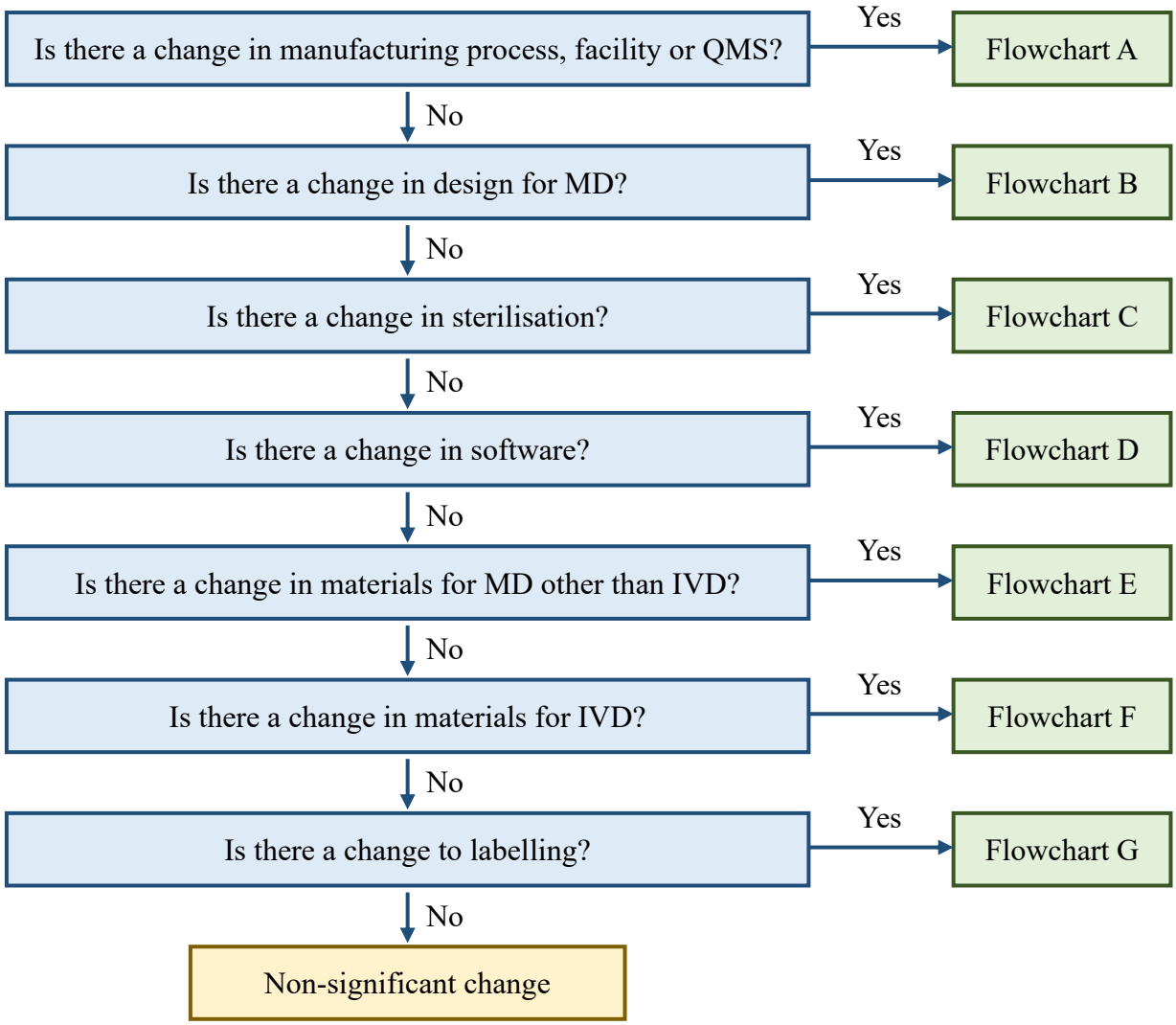
The **main flowchart** is a generalized discussion of the broad principles that can be used to determine if a change would affect the safety and/or performance of a medical device.

Flowchart A to G details specific questions and answers to assist in determining if a change is considered to be significant or non-significant. The accompanying discussions and flowcharts are intended to define the processes used to categorise the change.

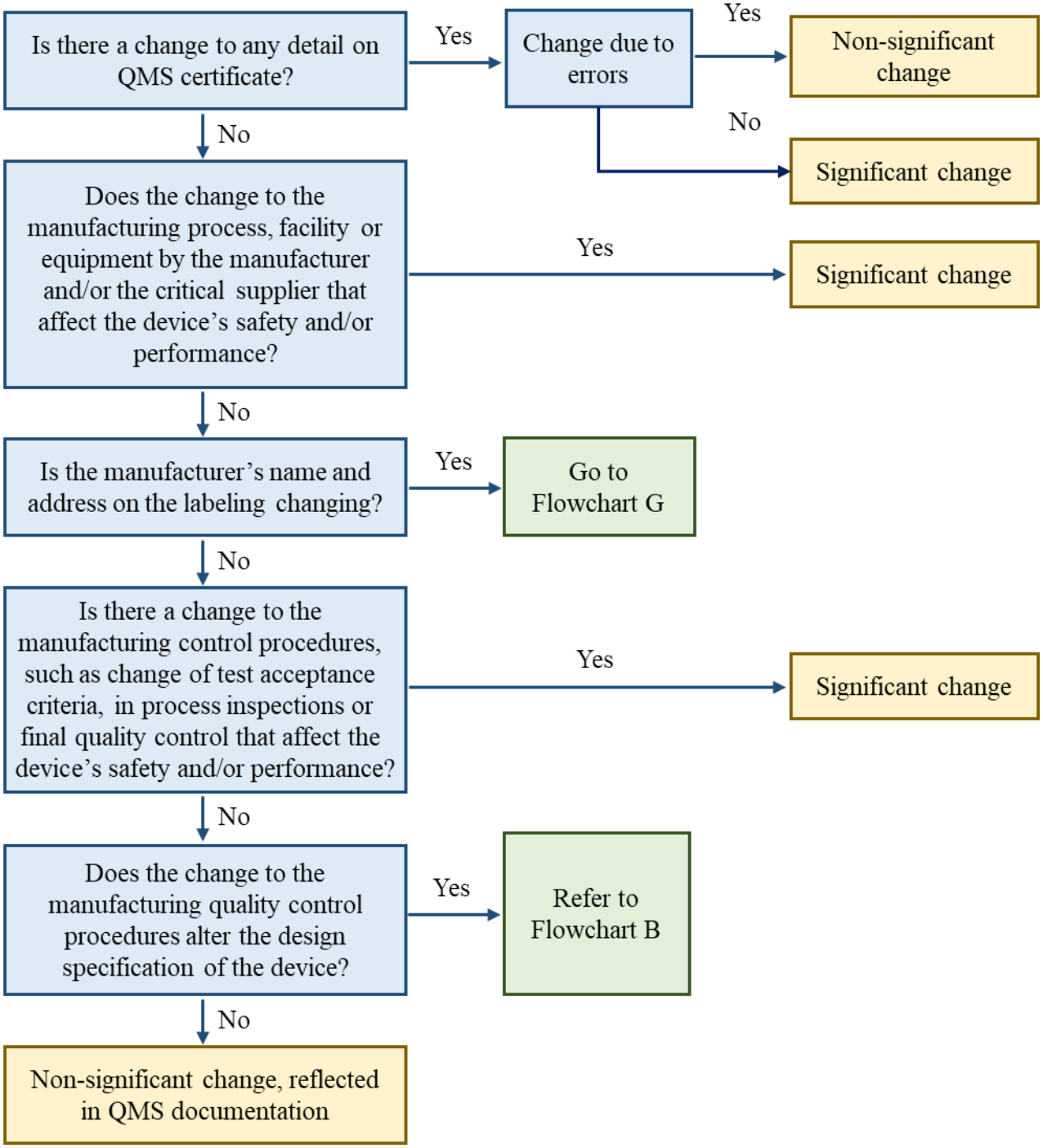
The following flowcharts are given.

- **Main Flowchart:** General Changes made to Medical Devices
- **Flowchart A:** Changes in Manufacturing Processes, Facility and/or Quality Management System (including QC)
- **Flowchart B:** Changes in Design for Medical Device
- **Flowchart C:** Changes to Sterilisation Facility and its Process and/or Quality Management System
- **Flowchart D:** Changes to Software
- **Flowchart E:** Changes in Materials for Medical Devices other than IVD
- **Flowchart F:** Changes in materials for IVD Medical Devices
- **Flowchart G:** Changes to Labelling

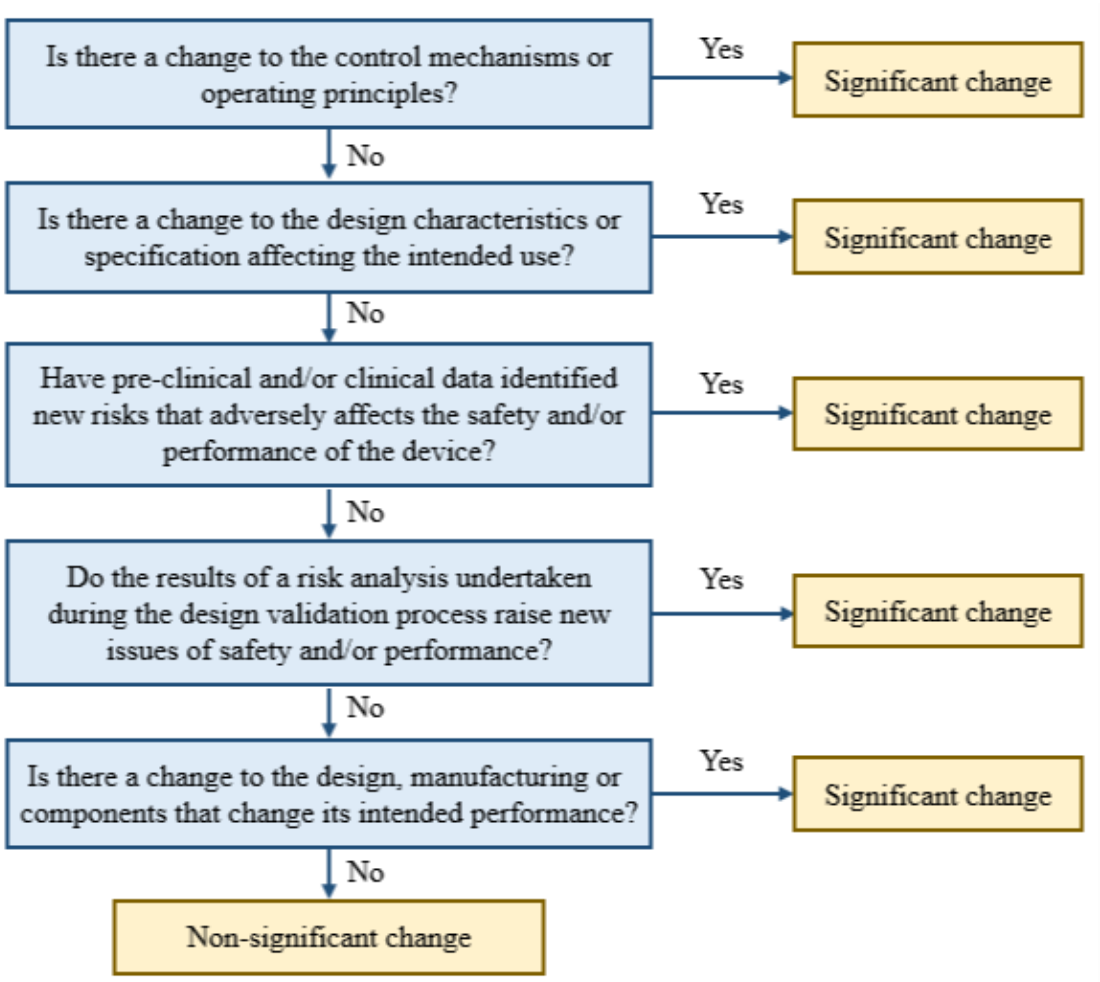
5.3.1 Main Flowchart: General Changes made to Medical Devices



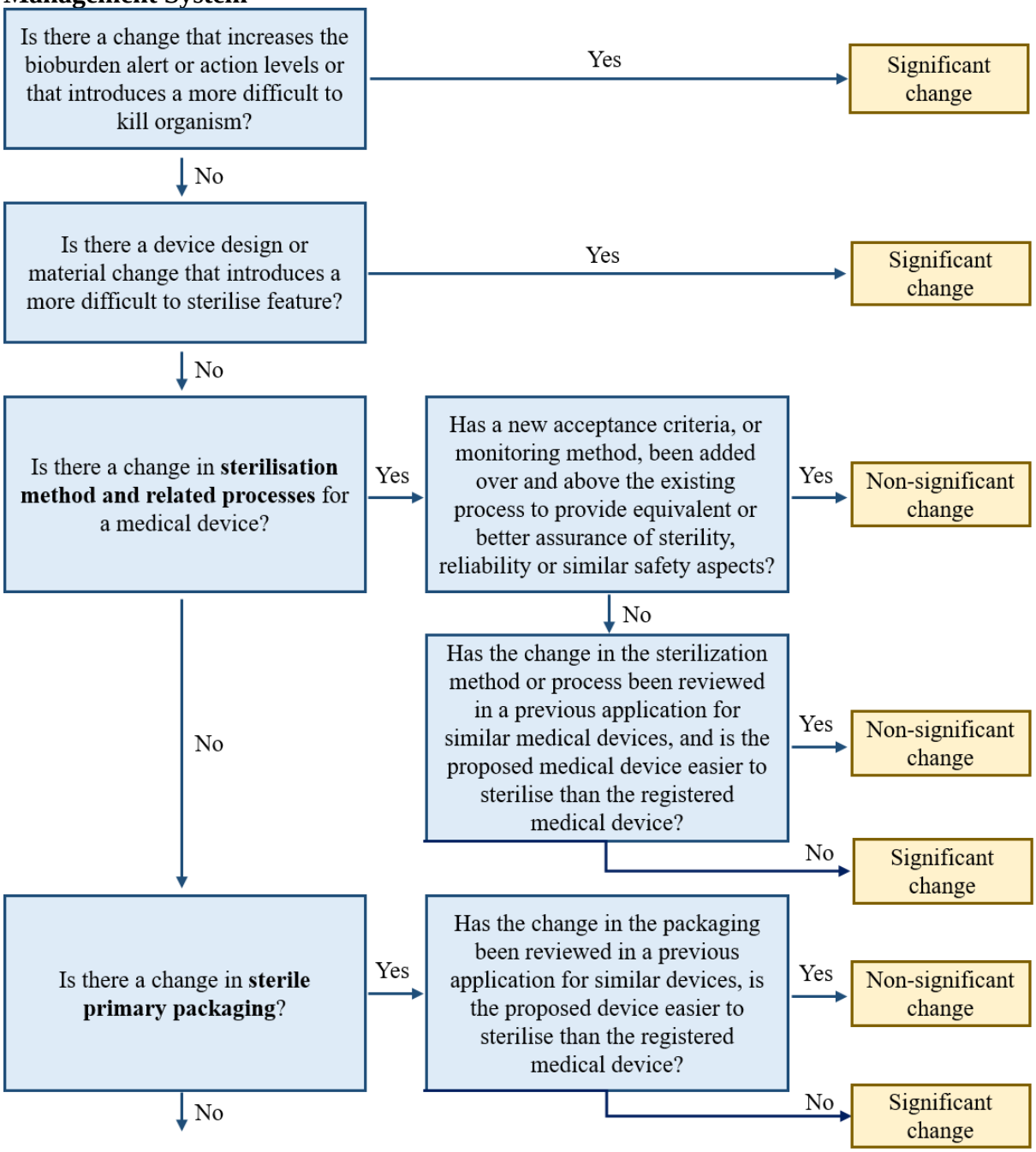
5.3.2 Flowchart A: Changes in Manufacturing Processes, Facility and/or Quality Management System (including QC)

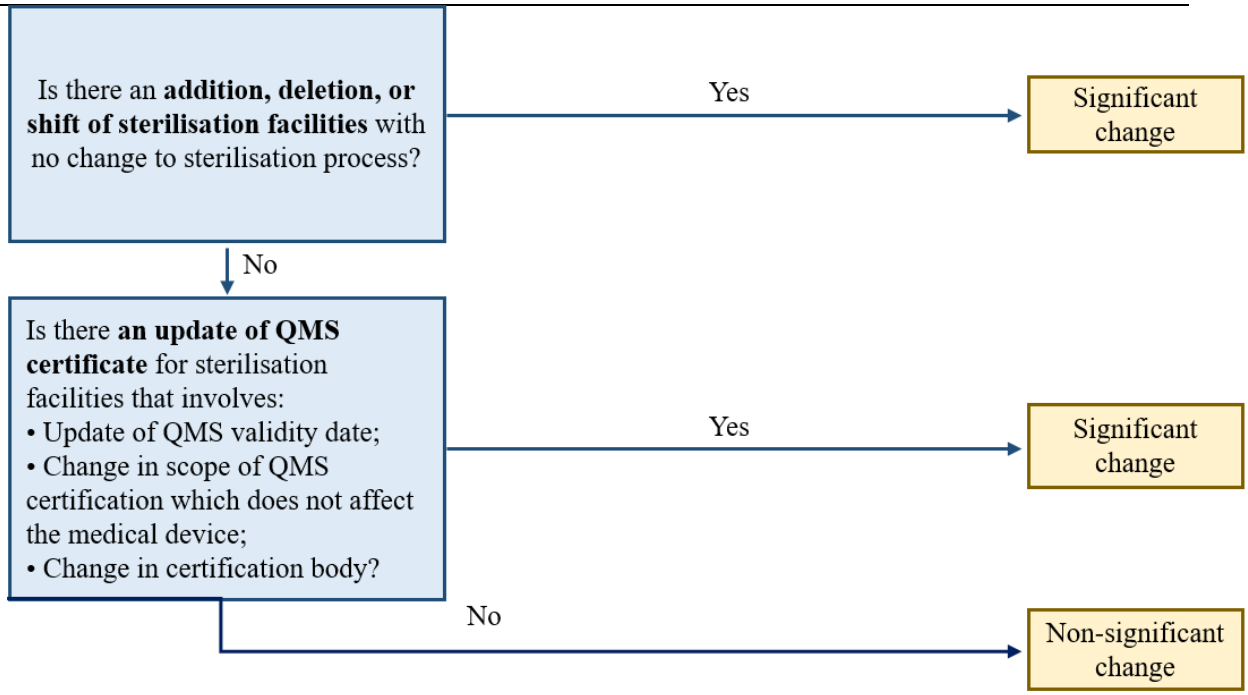


5.3.3 Flowchart B: Changes in Design for Medical Devices



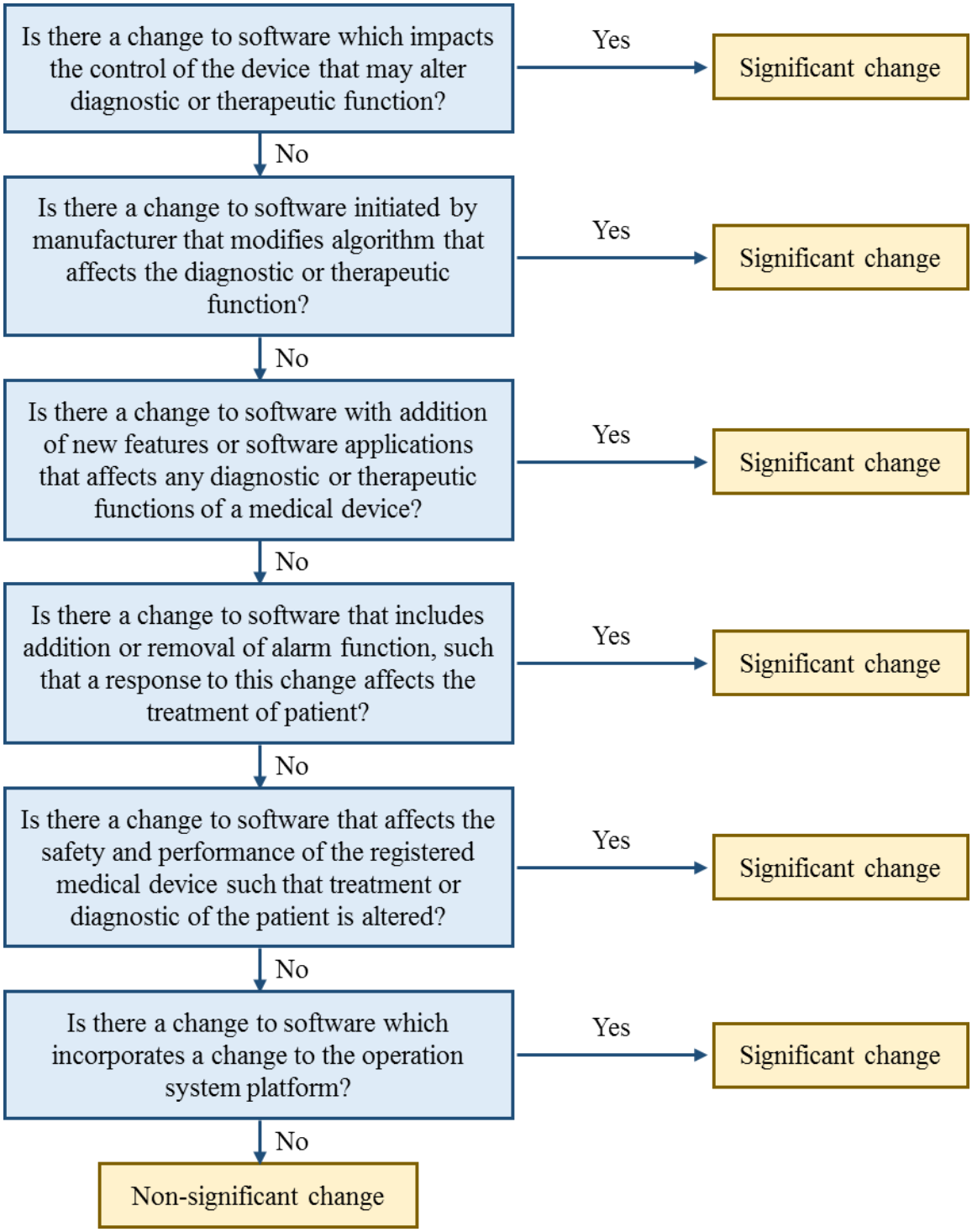
5.3.4 Flowchart C: Change to Sterilisation Facility and its Process and/or Quality Management System




Is there an addition, deletion, or shift of sterilisation facilities with no change to sterilisation process?
Yes
Significant change
No
Is there an update of QMS certificate for sterilisation facilities that involves:
• Update of QMS validity date;
• Change in scope of QMS certification which does not affect the medical device;
• Change in certification body?
Yes
Significant change
No
Non-significant change

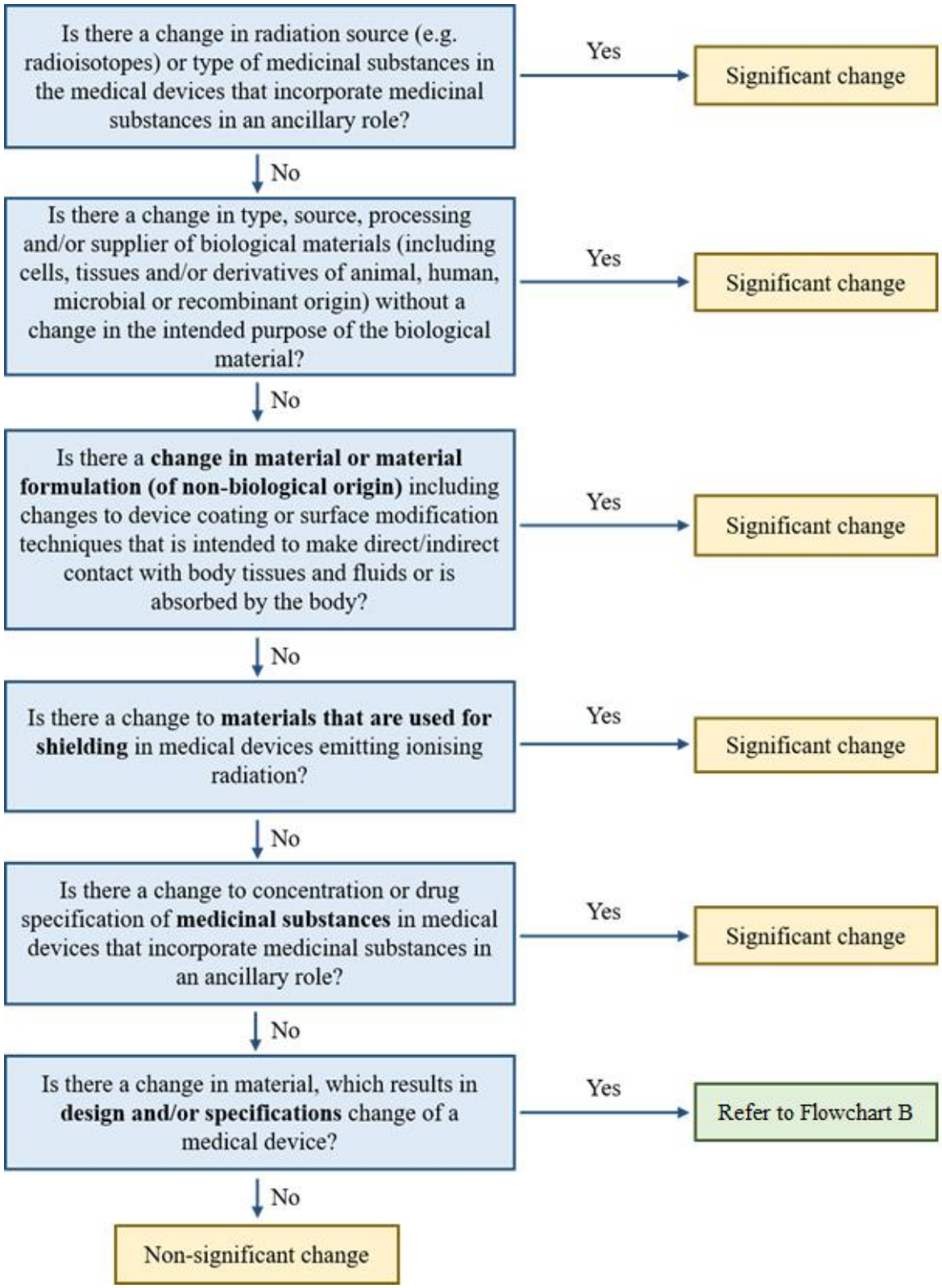
253

5.3.5 Flowchart D: Changes to Software



256 **5.3.6 Flowchart E: Changes in Materials for Medical Devices other than IVDs**

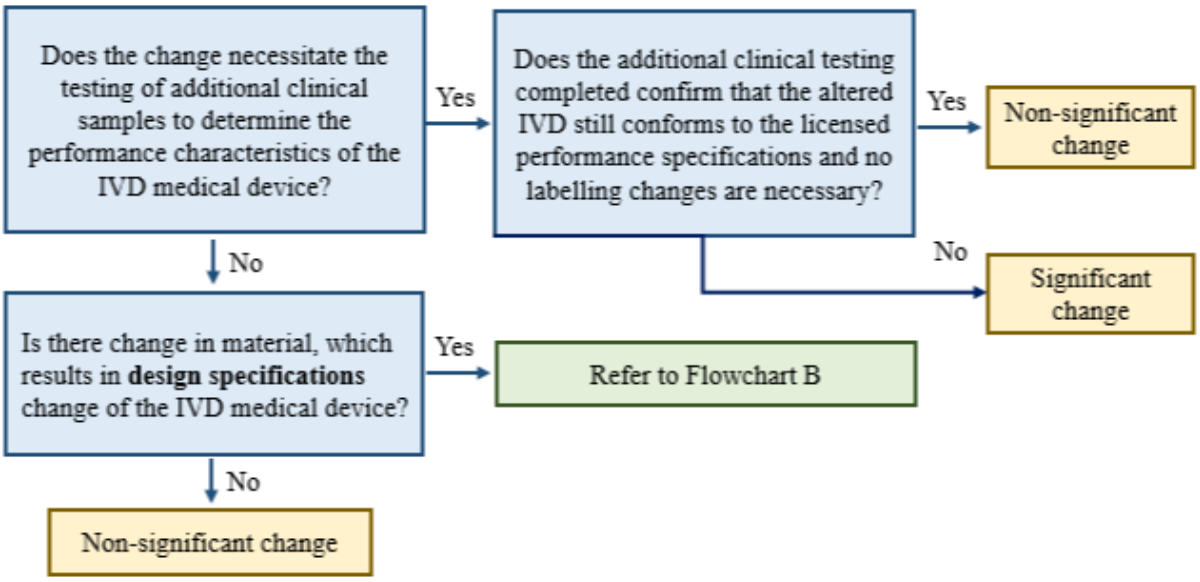
257



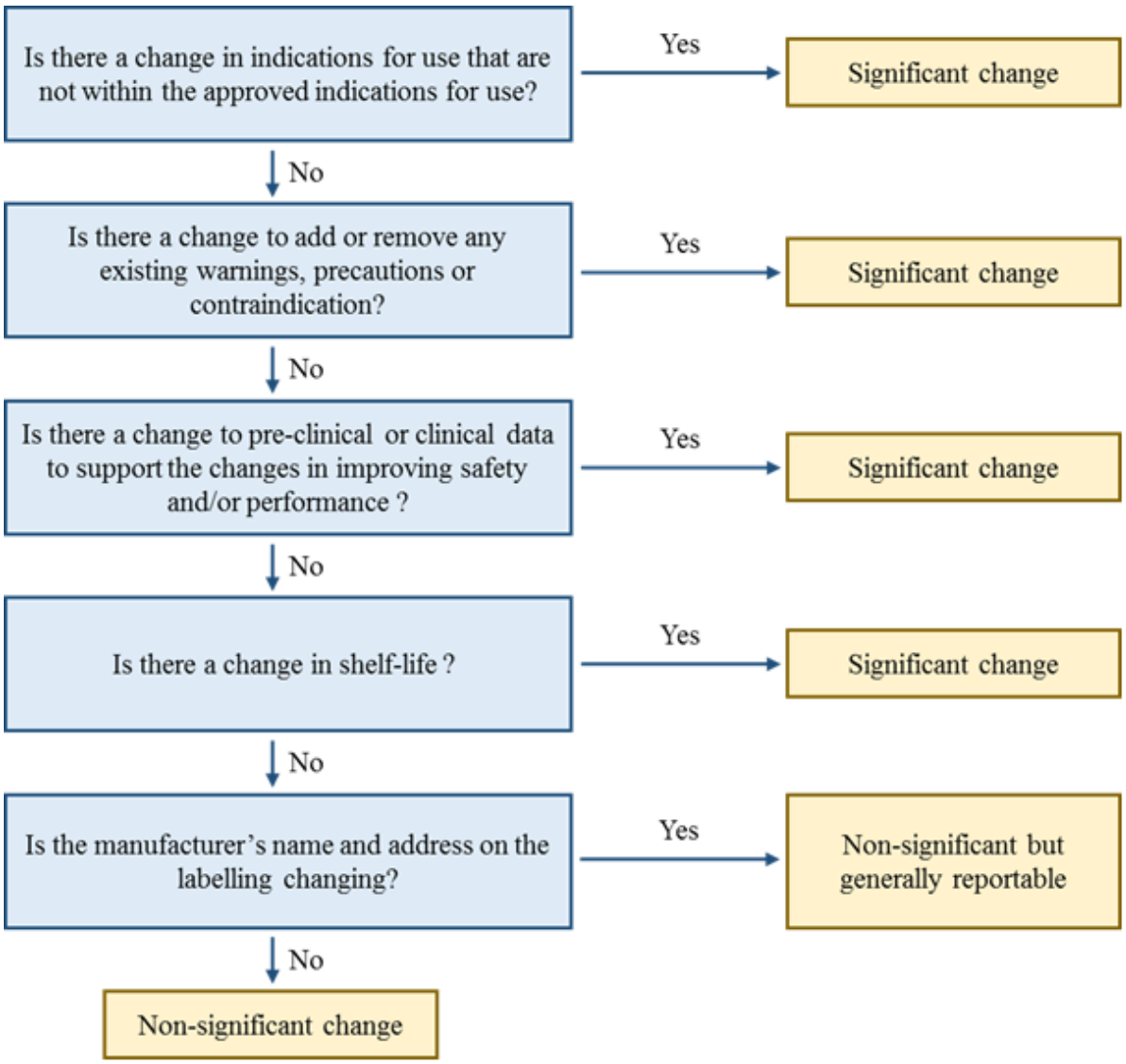
258

259

5.3.7Flowchart F: Changes in materials for IVD medical devices



5.3.8 Flowchart G: Changes to Labelling



5.4 Examples of changes and reporting requirements

5.4.1 Changes in manufacturing processes, facility and/or Quality Management System

Example	**Category (Significant, non-significant)**
Changes to QMS Certificate, such as: *Change/addition/removal of manufacturing site,* *Change of scope*	Significant
Change to manufacturing processes (including changes made to outsourced processes) that may affect the safety and/or performance of the medical device, such as: *Change in the equipment used for cutting, resulting in the change in length of sutures.* *Moulding or cutting manufacturing process* *Change of centrifugation to filtration process which results in better molecule separation.* *Change of implant manufacturing process from casting to 3D printing* *Change from manual operation to automatic operation, without changing the product specification*	Significant
Change in specification of registered medical device due to change in critical supplier, such as: *Change of the supplier of the Antibody with different manufacturing process.* *Change of supplier of plastic raw material of catheter.*	Significant
Changes to Manufacturing QC process issues, such as: *Removal of two test parameter and extend acceptance criteria*	Significant
Change of zip code on the certificate, typo errors and correction	Non-Significant
Changes to Manufacturing QC process, such as: *New QC specification with additional testing* *Change of measuring and/or monitoring equipment without changing test parameter*	Non-Significant
Change in non-critical supplier that extrudes the polymer tubing with no change in finished product performance specifications.	Non-significant

5.4.2 Changes in design for medical devices other than IVDs

Example	**Category (Significant, non-significant)**
All changes to the control mechanisms, operating principles and/or design characteristics of a medical device, such as: *Change from a quantitative assay to a qualitative assay* *Addition of a footswitch to an X-ray system that previously do not operate via a footswitch mechanism.* *Change of an RIA test to an ELISA test.*	Significant
Change in the design characteristics that allows for additional or broader intended use, such as: *A smaller sized hip prosthesis or fracture fixation screw that are significantly different from their predicate designs.* *Addition of urine as specimen in the intended use for creatinine test*	Significant
Change that have Pre-clinical and/or clinical data identified new risks that adversely affects the safety and/or performance of the device, such as: *The original heat-sealing package barrier found risk of leakage and change to sterile packaging barrier*	Significant
Change results of a risk analysis undertaken during the design validation process raise new issues of safety and/or performance, such as: *Change from an internal direct current (DC) power source to an external alternating current (AC) source or vice versa* *During the clinical validation process, ceramic dental cap has found durability issues, other materials has to be considered Change to the cable design and grip of a steerable ablation catheter, which results in improved deliverability and improved procedural times.*	Significant
Change to the design, manufacturing or components that change its intended performance, such as: *All changes in specifications (including shelf life and stability) of an IVD medical device*	Significant
Change of the secondary packaging	Non-significant
Change of colour of the cap of a reagent	Non-significant
Changes of smartphones and computers (including tablet PC) running medical software that does not accompany changes in the software	*Non-significant*
Changes of storage media (CD, USB, Web, etc.) of the standalone software that does not accompany changes in the software	*Non-significant*

5.4.3 Changes to sterilisation Facility and its Process and/or Quality Management System

Example	Category (Significant, non-significant)
Change of the sterilisation process, such as: *Change from ethylene oxide to gamma radiation sterilization*	Significant
Change that increases the bioburden alert or action levels or that introduces a more difficult to kill organism, such as a change that introduces additional pre-sterilisation transport steps.	Significant
Device design or material change that introduces a more difficult to sterilize feature, such as: *Change to the packaging where a single pouched sterile device is put into a double pouch.*	Significant
Change from biological indicator to parametric release or change from batch release to parametric release	Significant
Change in moist heat sterilisation parameters	Significant
Change from a pre-blended sterilant (EtO and CHCs) to EtO post-blended with nitrogen. The ultimate concentration of EtO in the sterilant is the same in both cycles.	Non-significant
Change from using Air (mixture of 80% Nitrogen and 20% Oxygen) to pure Nitrogen in the aeration process to avoid explosive gas mixtures.	Non-significant

5.4.4 Changes to Software

Example	**Category (Significant / Non-Significant)**
Change to software which impacts the control of the device that may be alter diagnostic or therapeutic function, such as: *Software change causing the change of critical steps for laser delivery on eye treatment*	Significant
Change to software initiated by manufacturer that modifies the algorithm that affects the diagnostic or therapeutic function, such as: *An X-ray Lung Nodule Assessment Software is used along with a Digital Radiography System to support physicians in the visualization, identification, evaluation and reporting of pulmonary lesions/nodules in chest images. An algorithm change improves the detection rate for small nodules.*	Significant
Change to software with addition of new features or software applications that affect any diagnostic or therapeutic functions of a medical device, such as: *Insulin Pump - Software changes that allow for wireless communication with compatible (continuous) blood glucose monitors.*	Significant
Change to software that includes addition or removal of alarm function, such that a response to this change affect the treatment of patient, such as: *Electrocardiogram Addition to software of an early warning alarm to signal a potential cardiac event such as atrial fibrillation.*	Significant
Change to software that affect the safety and performance of the registered medical device such that treatment or diagnostic of the patient is altered, such as: 1. *Blood Oxygen Monitor - A software change that allows the monitor to report blood CO2 concentrations with higher accuracy up to 0.5% deviation.* 2. *Upgrade of software version changes the performance characteristics like specificity or sensitivity of the In-vitro diagnostic medical device.*	Significant
A simple bug fix to correct the display error on the data table from the software analysis result.	Non-significant
Change in software which only introduces non-therapeutic and non-diagnostic features such as printing, faxing, improved image clarity or reporting format	Non-significant
Change in software to disable certain functions that does not interact with other functions	*Non-significant*

Change to software incorporating a change to the operation system platform, such as: *A change in the software together with operating system change from Linux to another operating system platform.*	Significant
Addition, change, and deletion of OS version(s) (operating environment) within the same platform such as: *When Windows X is added for a product for which Windows 7 is specified as an OS*	Non-significant
Change in software to alter colors and location of menu on graphic user interface of medical devices that does not affect safety and performance of the device but results in version change	Non-significant
Change in software to add languages for users that does not accompany changes in the main features and misunderstanding in translation for intended use, principle of operation, and performance	Non-significant
Change in the distribution/storage method of software among physical media (USB, CD, DVD), digital means (download), etc.	Non-significant
Change in software to strengthen the cybersecurity such as: *1. Adding encryption to the configuration file of the device,* *2. Adding passcode requirements for remote users, in addition to the password needed to access the device., and* *3. Adding a timeout for remote user or changing the access of the restricted user/customer to appropriate levels.*	Non-significant
Change in software to disallow use of the specific characters that are invalid as defined in the instrument host interface specification for the prevention of Specimen Identification (ID) barcode information truncation.	Non-significant
Change in software to return the system into specification of the most recently cleared device regarding DICOM(Digital Imaging and Communications in Medicine standard; http://dicom.nema.org/) conformance allowing the automatic fetching of prior studies from radiology information system using PACS (Picture Archiving and Communication System).	Non-significant
Change in software to correct the bottle size parameter of the cleaning solution to prevent the fluid detection errors.	Non-significant
Change in IVD analyzer software to ensure new data of the administrative records for reagents is not merged with the existing data in the table within the software by correcting software code in the control unit of the analyzer to modify the table to add new columns.	Non-significant

Change in IVD analyzer software to rewrite an incorrectly worded software requirement and to modify code in the control unit of the analyzer without modifying the core algorithm (such as detection or measurement module algorithm).	Non-significant
Changes in software including the addition of product indication for use or its operating principles including diagnostic algorithm such as machine learning that may alter diagnostic or therapeutic function.	Significant
Change in accuracy of Machine Learning Medical Device software via modification and expansion of the training dataset without any changes to labeled product design specification.	Non-Significant

277

278 **5.4.5 Changes in materials for medical devices, other than IVD medical devices**

Example	**Category (Significant, non-significant)**
Change in radiation source (e.g. radioisotopes) or type of medicinal substances in the medical devices that incorporate medicinal substances in an ancillary role, such as: *Change in the drug of a drug eluting stent*	Significant
Change in type, source, processing and/or supplier of biological materials (including cells, tissues and/or derivatives of animal, human, microbial or recombinant origin) without a change in the intended purpose of the biological material, such as: *Change in source of hyaluronic acid from Streptococcus zooepidemicus to Streptococcus equi*	Significant
change in material or material formulation (of non-biological origin) including changes to device coating or surface modification technique in a medical device that is intended to make direct/indirect contact with body tissues and fluids or is absorbed by the body, such as: *Peripherally Inserted Central Catheter (PICC)* *Introduction of a colorant change into the insertion hub of a PICC that is part of the fluid path for fluid administration or withdrawal from a patient.* *Cardiovascular Catheter* *A change of material to a cardiovascular catheter that comes in contact with body tissue (e.g. change to/from polyether block amide (PEBA), Polyamide or polyether ether ketone (PEEK).*	Significant
Change to concentration or drug specification of medicinal substances in medical devices that incorporate medicinal substances in an ancillary role, such as: *Change in the concentration of the drug in a drug eluting stent* *Change in the concentration of antibiotics or a change to a different antibiotic in a catheter coated with antibiotic Catheters that coated with antibiotics*	Significant
Change in supplier or vendor of the material, but the material meets the manufacturer's previously reviewed specification.	Non-significant
Peripherally Inserted Central Catheter (PICC) *Introduction of a colorant change into the flush port of a PICC. The flush port is an access port for flush syringes for IV line clearance or volume block and is not intended to be used for fluid administration or withdrawal from a patient.*	Non-significant

279

5.4.6 Changes in materials for IVD medical devices

Example	Category (Significant, non-significant)
Changes which need testing of additional samples, such as: *Change of sources or types of materials (conjugate, antibodies, antigens, primers or substrate)* *Change to the sample preparation, such as the inclusion of a stabilizer for an IVD that is intended to simplify preparation requirements or increase sample stability.*	Significant
Change in material, which results in design specifications change, such as: *Formulation change of reagents of test kits (buffer concentration, addition of preservatives)* *Change from a liquid to solid reagent and vice versa*	Significant
A change in supplier or vendor of the material, but the material meets the manufacturer's previously reviewed specification.	Non-significant
Change of sources of non-critical materials, such as magnesium stearate from an animal to vegetable source in a reagent of an IVD kit with no change in performance specification.	Non-significant

5.4.7 Changes to Labelling

Example	**Category (Significant, no-significant)**
All changes to the labelling of medical devices that involve addition, removal and/or revision of warnings, precautions and/or contraindications not arising due to safety and/or performance concerns	Significant
Labelling changes that modify the approved method of use; or involve a change from 'professional use only' to 'home use'	Significant
Change involves a reduction of intended use/indication of use not arising due to medical device safety and/or performance concerns	Non-significant, but generally reportable
Changes to the label due to typo error	Non-significant

6.0 Multiple Changes for one product

If multiple changes are made on a device at the same time, the assessment of each change should be made according to the flowcharts outlined in this guideline. If the changes are significant, the manufacturer may summarize all changes in one report and describe how the modified medical device differs from the previously registered device.

7.0 Reference to change approvals by other jurisdiction

If the manufacturer can provide proof that the proposed change has been assessed and accepted by another jurisdiction, the RA may make an informed decision of acceptance or rejection of the change based on abbreviated review or waive the review.