Global Harmonization Working Party
Towards Medical Device Harmonization

PROPOSED DOCUMENT

Title: Change Management to Registered Medical Devices

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Work Group 2, Pre-market: IVD
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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/effectiveness 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/effectiveness of the medical device.

According to the nature of the change, the Regulatory Authority (RA) will determine whether evidence of safety and/or performance/effectiveness 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

Risk based and harmonised worldwide requirements for managing changes to registered medical devices would offer significant benefits to the manufacturer, the users, the patients and the RAs. Eliminating or reducing differences between jurisdictions can decrease the cost of regulatory compliance activities, increases regulatory resource efficiencies for RAs and allows patients earlier access to new technologies and treatments.

2.2 Purpose

This document assists RAs and manufacturers in assessing and managing changes during the life cycle of medical devices. The document provides guidance on general principles, categorization, reporting, and alternative pathways for managing changes using a risk based approach with examples.

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 a Medical Device that appear within the AHWP 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 *Essential Principles of Safety and Performance of IVD Medical Devices.*

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

AHWP/WG2 /F001:2021 *AHWP Reagent Replacement and Instrument Family Policy*

US - Guidance for Industry and Food and Drug Administration Staff, Deciding When to Submit a 510(k) for a Change to an Existing Device - October 25, 2017

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

US - Guidance for Industry and Food and Drug Administration Staff, Replacement Reagent and Instrument Family Policy - December 11, 2003

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

US - Guidance for Industry and Food and Drug Administration Staff -Changes to an Approved Application: Biological Products - July, 1997

US - Draft Guidance for Industry and Food and Drug Administration Staff – Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions – April 2023

US - Guidance for Industry and Food and Drug Administration Staff - Replacement Reagent and Instrument Family Policy for In Vitro Diagnostic Devices August 17, 2022

US - Guidance for Industry and Food and Drug Administration Staff - Assay Migration Studies for In Vitro Diagnostic Devices, April 2013

Canada - Guidance for the Interpretation of Significant Change of a Medical Device, January 20, 2011

Japan - Guideline of authorization and review for major change in IVD (issued in 2015), applicable to IVD

Japan - MHLW/PMDA Predetermined Change Control Plan Approach - Improvement Design within Approval for Timely Evaluation and Notice- Digital Health Regulation In Asia-Pacific. Overview and Best Practices. APACMed Digital Health Committee. Regulatory Working Group. 2021

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

Singapore - Medical Device Guidance- GN-21 - Guidance on Change Notification on Registered Medical Devices, Revision 5, March 2023

Singapore - Regulatory Guidelines for Software Medical Devices – A Life Cycle Approach, Revision 2, April 2022

Singapore - Medical Device Guidance- GN-12-1 - Guidance on Grouping of Medical Devices for Product Registration – General Grouping Criteria, Revision 2.1, November 2017

Kingdom of Saudi Arabia - MDS-G-012-V1/230322 - Guidance on MDMA Significant And Non-Significant Changes

Malaysia- MDA/GD/0020 - Change Notification for Registered Medical Device, Fourth Edition, 21 November 2022

Australia - Changes affecting TGA-issued conformity assessment certificates - Guidelines for notifying the TGA about ‘substantial changes’ to, or transfers of, conformity assessment certificates, Version 2.0, August 2021

EU - MDCG 2020-3 Rev 1. Guidance on significant changes regarding the transitional provision under Article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD, May 2023

EU - MDCG 2022-20 - Substantial modification of performance study under the In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 - December 2022

South Korea - Guidance for Review and Approval of Artificial Intelligence-based Medical Devices, May 2022

South Korea - "Guidance for Approval and Evaluation of Reagent of the Family *In Vitro* Diagnostic Devices", August, 2015

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

South Korea - Guidance for Change Management of IVD Medical Device, 5th version, March 2019

South Korea - Act on Nurturing Medical Devices Industry and Supporting Innovative Medical Devices, August,2021

South Korea - Guidance for Precertification of Innovative Medical Devices, October-2021

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

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

WHO - Annex 3 - WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices, WHO Medical device technical series, Replacement of Annex 4 of WHO Technical Report Series, No. 1003

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'"

Software as a Medical Device– The term is as defined in AHWP/WG3/F001:2015 Guidance Document on Medical Device Software - Qualification and Classification

AI/ML– The term is as defined in IMDRF/AIMD WG/N67 Machine Learning-enabled Medical Devices- Key Terms and Definitions as Machine Learning-enabled Medical Device (MLMD) A medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose

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.

Intended use/intended purpose - The term is as defined in *GHTF/SG1/N045:2008 / GHTF/SG1/N68:2012 / GHTF/SG1/N70:2011 / GHTF/SG1/N77:2012 / GHTF/SG5/N6:2012*

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

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

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 claimed compliance with ISO 13485 or its equivalent of the part the management system with regard to quality.

Regulatory Authority- 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 devices marketed within its jurisdiction comply with legal requirements. (AHWP/-WG2-WG8/F002:2014

Risk Management - is a systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk (ISO 14971:2019 Medical devices -- Application of risk management to medical devices)

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

Recognition - The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference health authority is sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Reliance - The act whereby the National Regulatory Authority (NRA) (defined as Regulatory Authority in this document) in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others. (WHO definition - Good reliance practices in regulatory decision-making: high-level principles and recommendations)

Reference Agency /Reference regulatory authority – A supranational, national or regional authority or a trusted authority such as WHO prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions. (WHO definition - Good reliance practices in regulatory decision-making: high-level principles and recommendations)

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

System – A medical device system comprises of a number of medical devices/IVD medical devices and/or accessories that are: from the same product owner/manufacturer, intended to be used in combination to achieve a common intended purpose, compatible when used as a system and sold under a single system name or the labelling, IFU, brochures or catalogues for each constituent component indicates that the constituent component is intended to be used together or for use with the system (Singapore- Medical Device Guidance- GN-12-1 - Guidance on Grouping of Medical Devices for Product Registration – General Grouping Criteria)

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

5.0 General Principles

For any change made to an approved or registered Medical Device, In Vitro Diagnostic (IVD) Medical Device and Software as a Medical Device , the manufacturer must consider the device in question, the impact of the change on the patient, practitioner and/or user of the device, and the impact of the change on the intended use/indication for use, risk classification, and the specifications of the device, and decide whether the change could reasonably be expected to affect the safety and/or performance/effectiveness of the device and risk-benefit associated throughout its lifecycle.

In the case of multiple simultaneous changes, this guidance document should be utilized to aid in the assessment of each change individually, as well as to evaluate the cumulative impact of all changes collectively. Concurrently, a risk assessment should be conducted to ensure a comprehensive review and implementation of mitigation means.

There may be instances where the standard regulatory framework is inadequate for addressing unique characteristics of emerging technologies, therefore effective risk analysis approach should be considered by regulatory authorities to address these novel challenges.

The following sections give guidelines on assessment and categorisation, reporting and innovative pathways for changes

6.0 Categorisation and Assessment of Changes

6.1 Categorisation of Changes

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

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

Significant changes can include changes to any of the following:

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

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** that will not affect safety and/or performance/effectiveness of the medical device.

6.2 Tools to Assess Changes and the Way of Reporting

The following section presents flowcharts to assist manufacturers when assessing whether a change is considered 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/effectiveness of a Medical Device, In Vitro Diagnostic (IVD) Medical Device and Software as a Medical Device.

Flowchart A to F details specific questions and answers to assist in determining if a change is considered 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 in Appendix 1.

- **Main Flowchart:** General Changes made to Medical Devices and In Vitro Diagnostic (IVD) Medical Devices
- **Flowchart A:** Changes in Manufacturing Processes, Facility and/or Quality Management System (including QC) for Medical Devices and In Vitro Diagnostic (IVD) Medical Devices
- **Flowchart B:** Changes in Design for Medical Devices and In Vitro Diagnostic (IVD) Medical Devices
- **Flowchart C:** Changes to Sterilisation Facility and its Process and/or Quality Management System
- **Flowchart D:** Changes to Software for Medical Devices
- **Flowchart E1:** Changes in Materials for Medical Devices
- **Flowchart E2:** Changes in Materials for In Vitro Diagnostic (IVD) Medical Devices
- **Flowchart F:** Changes to Labelling of Medical Devices and In Vitro Diagnostic (IVD) Medical Devices

7.0 Reporting of Changes

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

It is recommended that the regulatory authority take **a risk-based approach in change management reporting** and prioritize resources to focus on **higher risk products with significant changes** that raise the highest risk to patients to ensure optimal efficiency of regulatory resources.

"Significant changes" should be reported to the RA prior to implementation of the change with supporting documentation to show the device is still safe and performing as intended.

"Non-Significant changes" are not normally reported to the RA prior to implementation of the change, 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 and product documentation.

Table 1 depicts the recommended risk-based approach in reporting of changes.

A manufacturer is required to submit a license amendment or change registration to Regulatory Authority for review and approval once they have determined that the proposed change to a higher-risk medical device is a significant change. For higher-risk devices with significant changes, manufacturers may sell and/or import the modified medical device in the market, only upon receipt of approval of changes by the regulatory authority.

Note: The need to report changes prior to implementation vs reporting post-implementation can depend on factors such as the type of change and regional requirements.

Table 1: Recommended Risk-Based Approach in Reporting of Changes

<table>
<tr><th>Product Risk Classification</th><th>Non-Significant Changes</th><th>Significant Changes</th></tr>
<tr><td>Low risk</td><td rowspan="4">No submission required
Change to be documented in QM</td><td>No submission required/documented in QMS</td></tr>
<tr><td>Medium risk</td><td>Change registration or change notification required (change notification with immediate implementation is recommended)</td></tr>
<tr><td>Medium/High Risk</td><td rowspan="2">License amendment or change registration required (change submission with RA approval recommended)</td></tr>
<tr><td>High risk</td></tr>
<tr><td colspan="3">Note 1: In some jurisdictions, all changes whether significant or non-significant may need to be reported, hence it is recommended to consult local jurisdiction and guidance on the reporting requirements
Note 2: QMS requirement: Manufacturer should
assess the change
perform risk benefit of the product
document the change and if applicable update the technical documentation</td></tr>
</table>

7.1 Bundling of Changes

7.1.1 Multiple changes on a device at the same time

It is recommended 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.

A significant change is only one type of change that may require a manufacturer to obtain an amended medical device license or change registration approval. When several successive or simultaneous changes are being considered in the evolution of a licensed device, this guidance document should be used to assess each change separately, as well as the collective impact of the changes. A side-by-side comparison of the proposed changes to the currently licensed device may be useful.

Hence, it is recommended that regulatory authorities **allow the submission of multiple changes to the same product in a single submission** to enable assessment the collective impact of the changes.

7.1.2 Single/same change to multiple products

If the same general simple change such as legal entity name change, legal manufacturer's address and other changes happen to multiple products of a manufacturer, the change across the products may be bundled to register or report once for all in a single submission.

Additionally in cases where the medical device is licensed as a **system**, changes may be proposed to one or more of the component parts. This document should be used to assess each change separately, as well as the collective impact of the changes.

7.2 Supplementary Submission

It is recommended that regulatory authorities allow the submission of other changes to the same product or product group, which is under RA review for a prior change or license renewal. RAs allow to review one change to a given device while other changes to that same device are under review. The newly submitted change should not be predicated on regulatory acceptance of the prior change (because regulatory acceptance of the earlier change cannot be assumed)

Note: Each change should not affect each other

7.3 Transition Measures and Time Period for Change Implementation

It is recommended for regulatory authorities to allow a reasonable transition period for manufacturers to transition from the old version to the new version. During such transition period, **import and/or sales/distribution of both versions should be allowed** to facilitate smooth transition as well as ensure supply continuity. Both versions of the medical device have to conform to the Essential Requirements for Safety and Performance for medical devices as stipulated in the *Regulations*.

When there are multiple versions of a device legally available, perhaps due to marketing both or because one is going through such a transition period, it should be clear how patients/users will be informed of the version of the device they are using/have access to and any necessary information about the differences

Hence, the manufacturer shall ensure that appropriate mechanisms are in place to differentiate and identify the changed device from the original version based on device or manufacturing attributes (e.g. through batch/ lot/ serial number and manufacturing date), and maintain relevant inventory records on file to ensure traceability of both versions as part of their QMS requirements. All relevant records on file shall be made available to the RA upon request.

8.0 Innovative Pathways for Changes

As the technologies evolve, so do the regulatory science, RA may consider innovative pathways for changes where appropriate on a risk-based approach.

8.1 Reliance/Recognition

As indicated in the WHO Guidance for Good Reliance Practice, reliance models are recommended for regulatory authorities to handle both pre-market and post market responsibilities related to the device full life cycle, including product changes.

Hence, it is recommended that regulatory authorities could recognize change approvals from **a reference agency** in order to facilitate local access to more rapid innovation. This may require Mutual Recognition Agreements. Where some Regulatory Authorities may not directly recognize approvals by **a reference agency**, they could still rely on evidence used in a device change previously approved by another regulator in order to reduce duplicative efforts, as well as the time and resources needed for review.

8.2 Replacement Reagent and Instrument Family Policy

Additional innovative review pathways are also encouraged to expedite device availability for patients. For example, the ***GHWP Replacement Reagent and Instrument Family Policy*** expedites availability of medium risk assays onto instruments within the same family. Assay Migration provides a more efficient pathway to migrate a assay to a new, already cleared instrument by leveraging a limited dataset.

The Reagent Replacement Policy is a risk-based approach that relies on the manufacturer's Quality Management System (QMS), including risk-based assessments, and criteria, testing, and internal documentation for each reagent application, to allow a portfolio or "menu" of low or medium risk reagents to be moved to a previously approved instrument or an instrument in the instrument family.

In the Instrument Family Policy an instrument can be added to an already existing Instrument Family. In turn, the Instrument Family allows the Replacement Reagent Policy to take effect.

For adding either an approved test kit/assay to a previously approved instrument (Replacement Reagent Policy), or a new instrument family member to a previously approved instrument family (Instrument Family Policy), please refer to the GHWP guidance document on ***The Replacement Reagent and Instrument Family Policy***.

8.3 Simplified Change Management of Software as Medical Devices

Given the need to frequently update and localise software, a simplified change management framework can enable agile modifications while maintaining a high-level of safety. Changes to software as medical devices can be managed by restricting the scope that needs regulatory review, limiting it to changes that relate to major functions, such as analysis algorithms (analysis methods), development language, operating environment, or communication functions. Other changes can be reasonably reported after the modifications have been implemented (South Korea - Regulations on Approval, Notification, Review of Medical Devices, June-2023)

8.4 Pre-determined Change Management Protocol (PCMP) of Software as Medical Devices

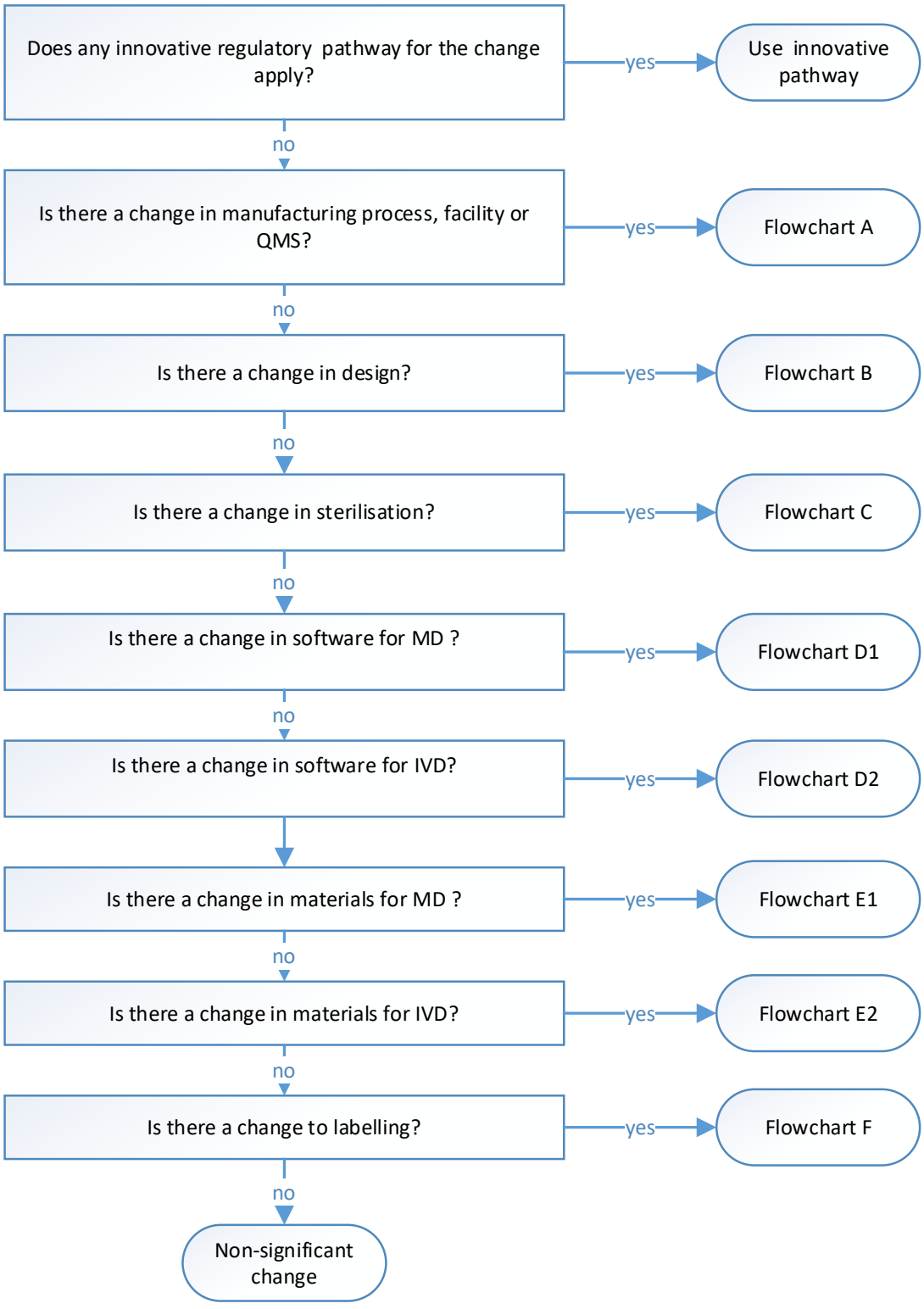
Pre-determined Change Management Protocols (PCMP) allow regulators to review a list of proposed changes, a change protocol (how the change will be implemented) and related acceptance criteria during the initial premarket review, essentially pre-approving the change as long as the protocol and criteria are followed. PCMP serves as an "agreement" between a manufacturer and regulator that, if the manufacturer follows the protocol for changes within its scope and meets the agreed upon criteria, the manufacturer can implement the modification without further regulatory review. (US Draft Guidance for Industry and Food and Drug Administration Staff – Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions – April 2023)

8.5 (Pre)certification Program for Innovative Medical Device Manufacturer

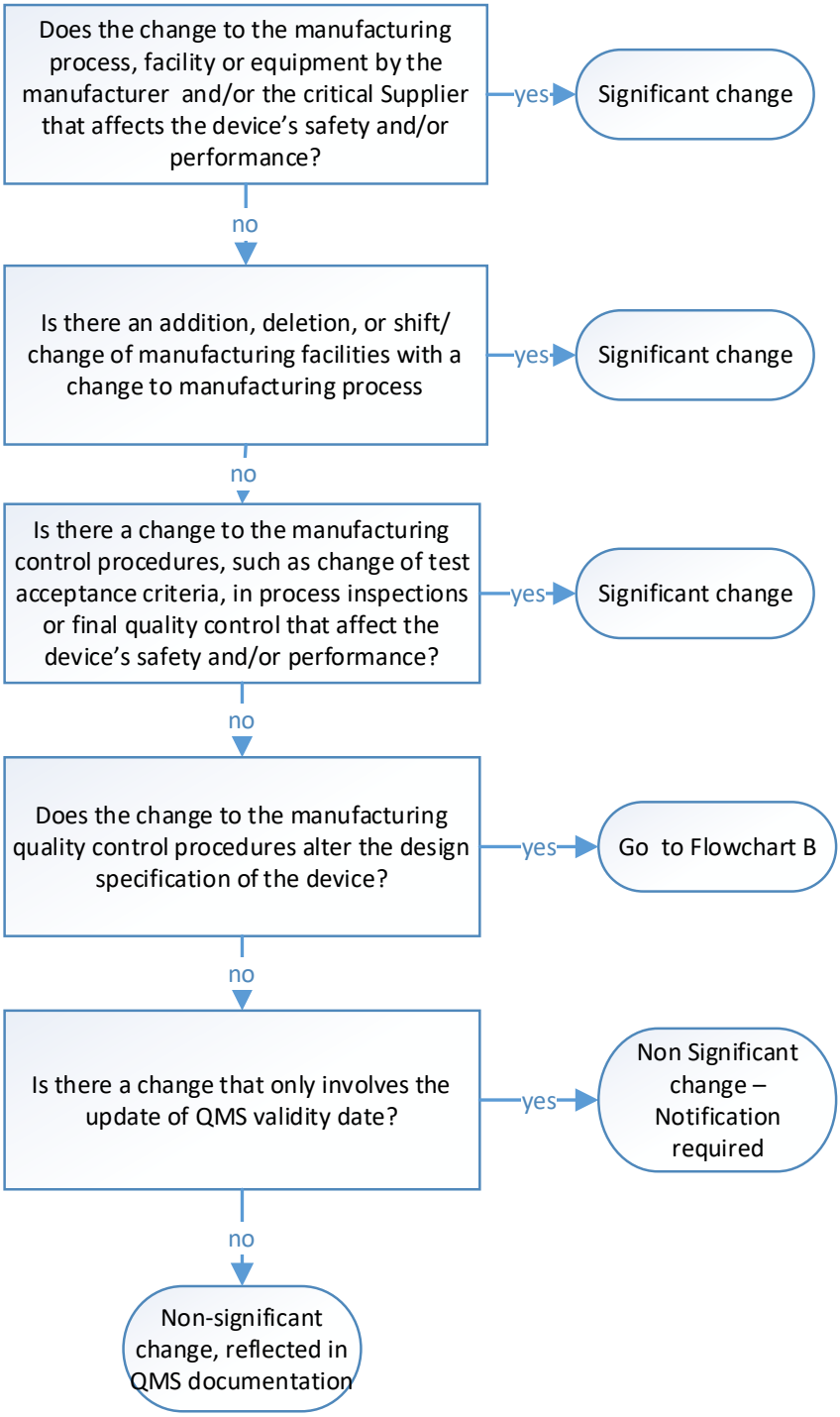
Innovative Medical Devices refer to medical devices that meet an unmet clinical need or meet a need in a way that is superior to existing methods in terms of safety and effectiveness. Innovative Medical Devices can be designated by regulatory authorities to encourage and assist their development in a number of ways (for example, as a breakthrough device). Additionally, manufacturers that can demonstrate excellence in consistently developing devices to a high-standard of safety may also be recognised and given further flexibility, this process has been precertification in a US FDA pilot programme.

9.0 APPENDIX 1 - Flowcharts

Main Flowchart: General Changes made to Medical Devices and In Vitro Diagnostic (IVD) Medical Devices



Flowchart A: Changes in Manufacturing Processes, Facility and/or Quality Management System (including QC) for Medical Devices and In Vitro Diagnostic (IVD) Medical Devices



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522 ***Flowchart B: Changes in Design for Medical Devices and In Vitro Diagnostic (IVD)***
523 ***Medical Devices***

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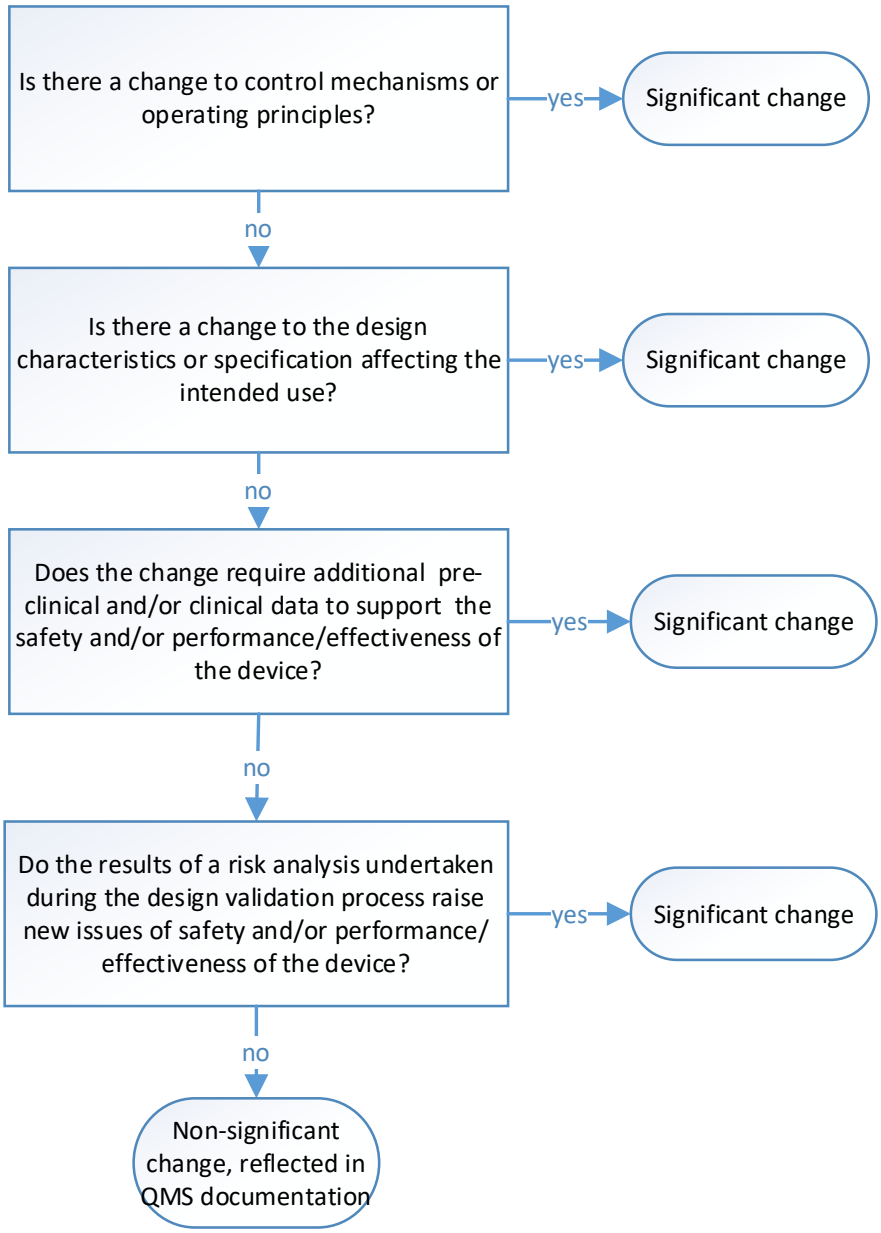

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528 ***Flowchart C: Change to Sterilisation Facility and its Process and/or Quality Management***
529 ***System***

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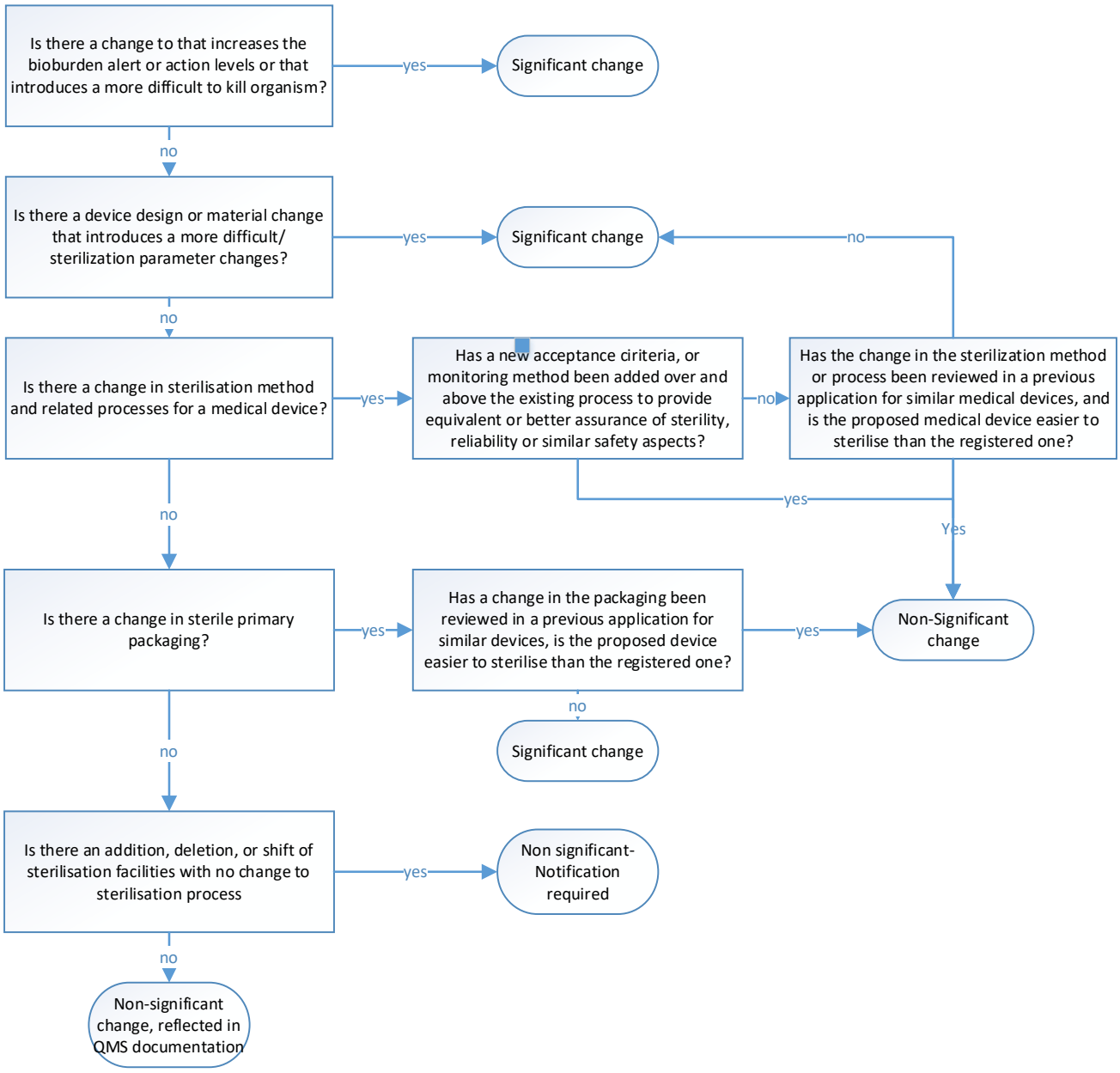

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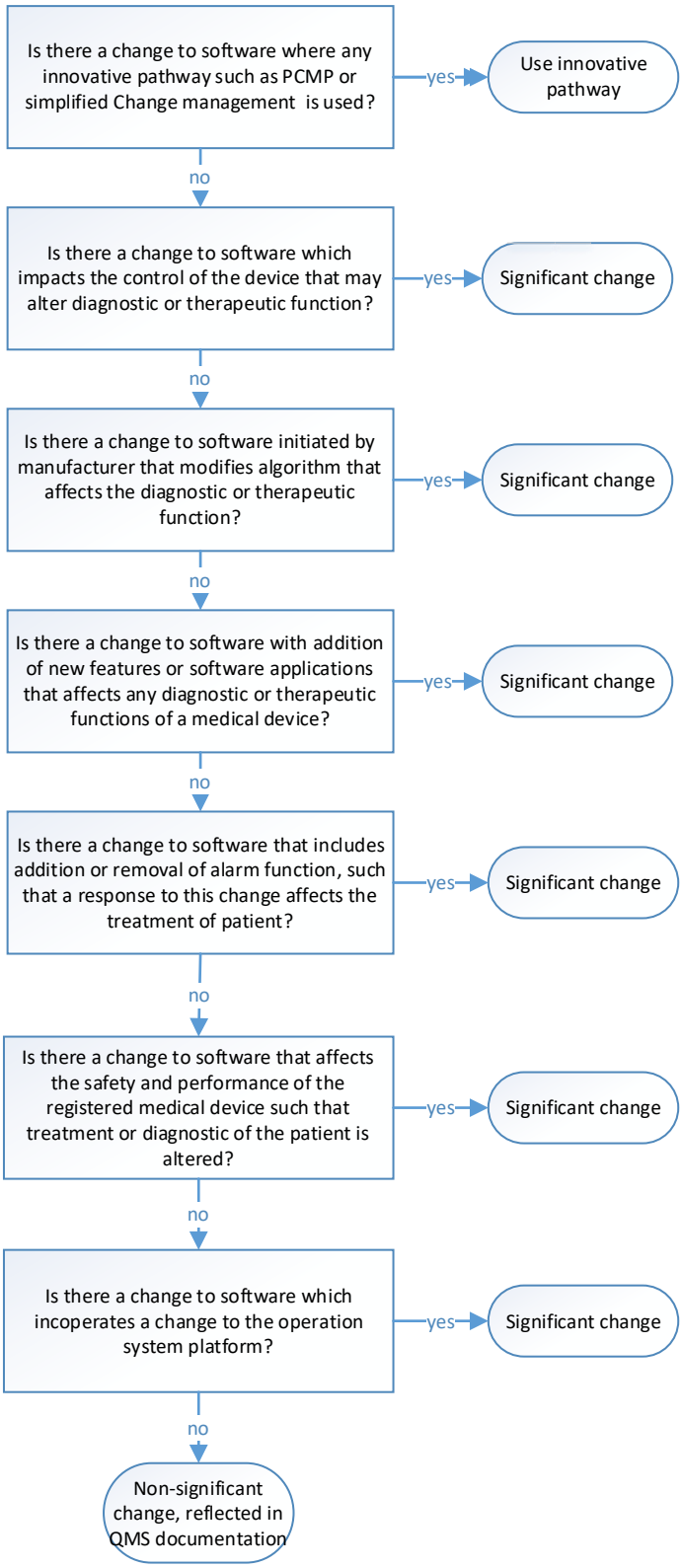
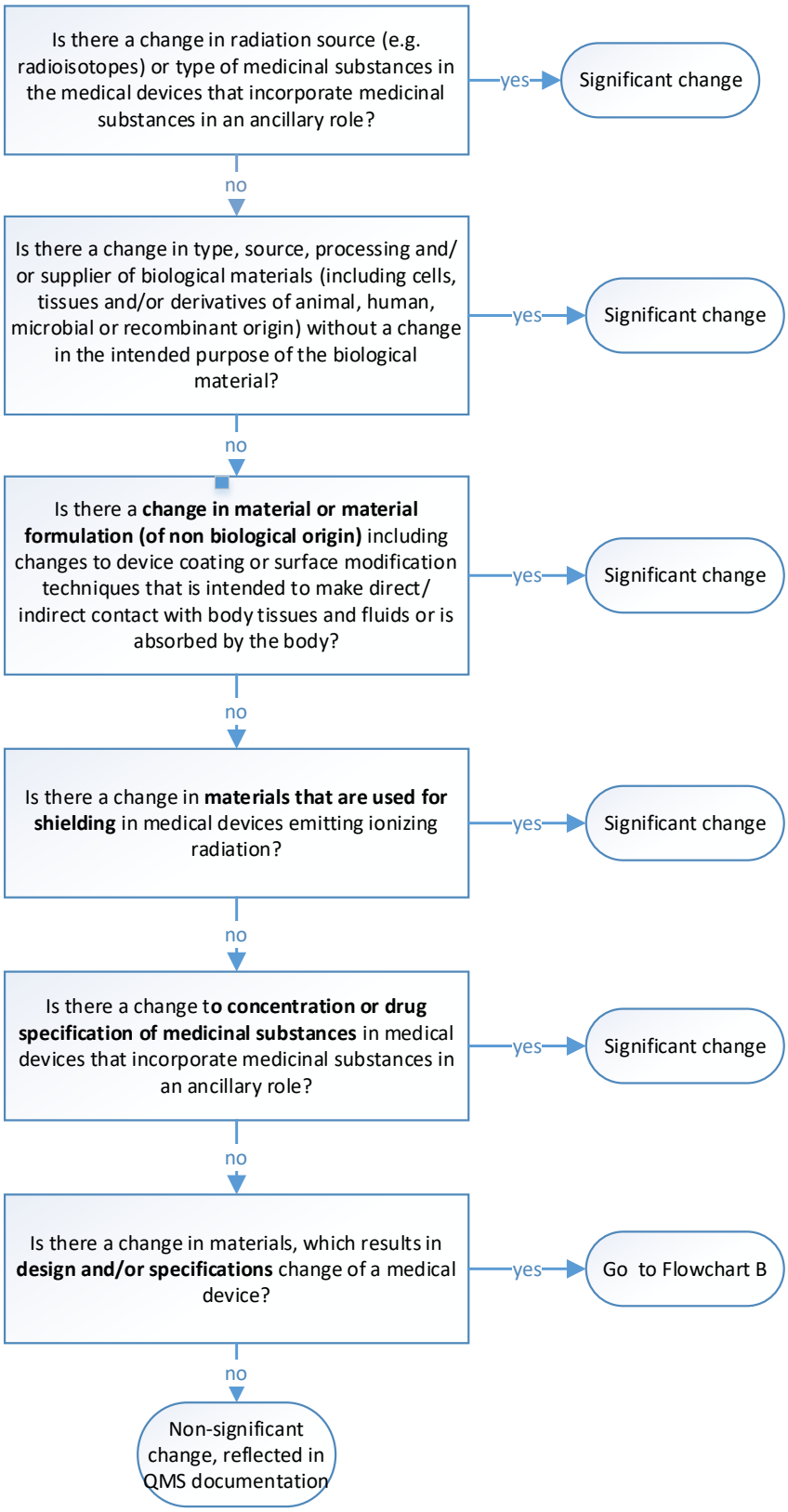
Flowchart D: Changes to Software for Medical Devices

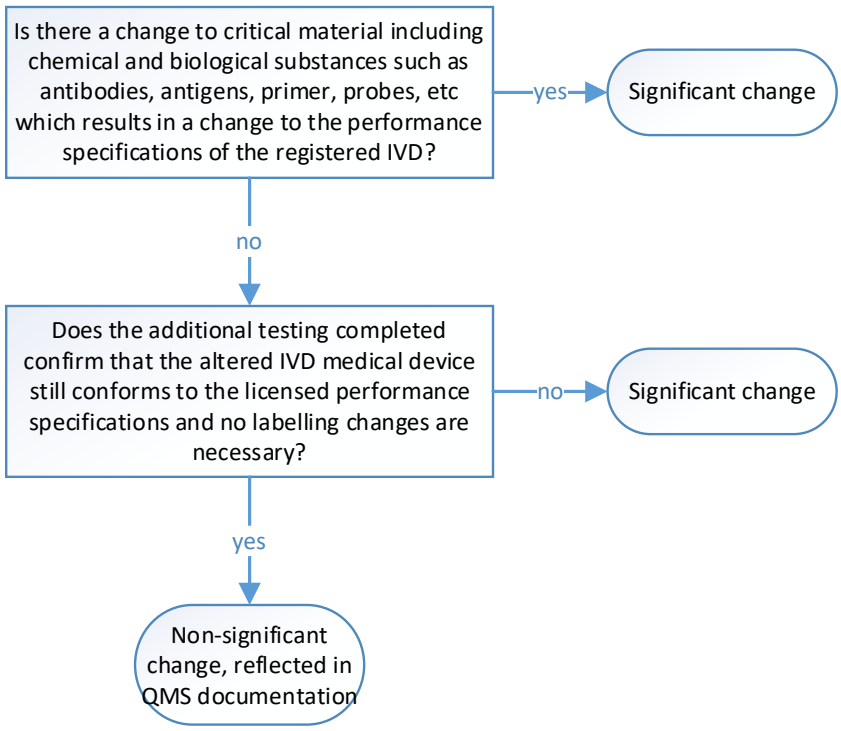
***** Software refers to Software as medical device and/or Software embedded/Software in Medical Device in medical device system.



Flowchart E1: Changes in materials for Medical Devices



Flowchart E2: Changes in materials for In Vitro Diagnostic (IVD) medical devices



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557 ***Flowchart F: Changes to Labelling of Medical Devices and In Vitro Diagnostic (IVD)***
558 ***Medical Devices***

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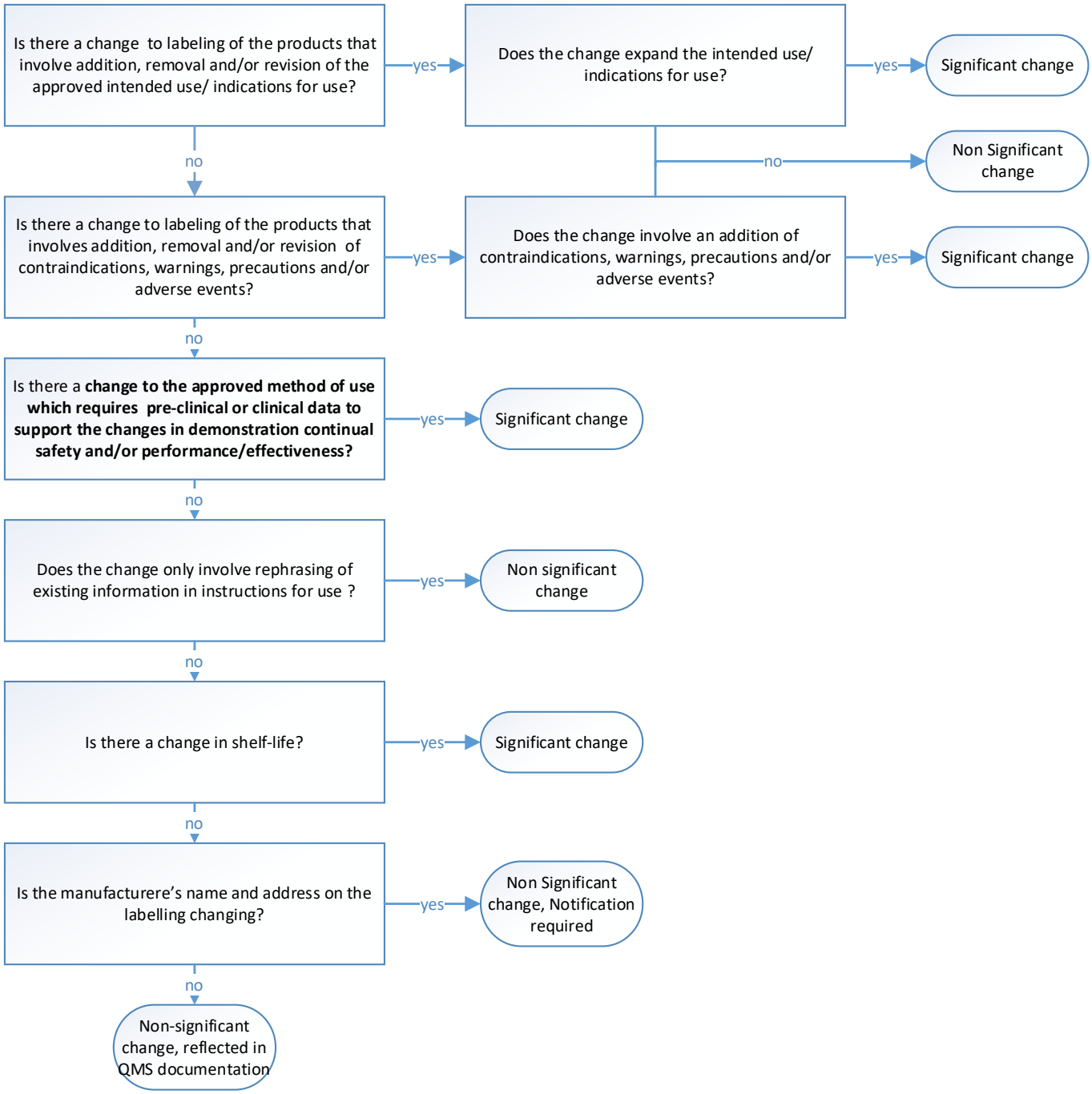

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10.0 APPENDIX 2 -Examples of changes and reporting requirements

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/effectiveness 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 in biological components sources or biological manufacturing processes in general* *Change of supplier of plastic raw material of catheter.* *Change of supplier of biological component with different manufacturing process*	Significant
Changes to Manufacturing QC process issues, such as: *Removal of two test parameter or modification of acceptance criteria, change in the sampling processes for QC testing*	Significant
Changes to QMS Certificate, such as: *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
Changes to Manufacturing QC process issues, such as: *Change in non-critical supplier that extrudes the polymer tubing with no change in finished product performance specifications.*	Non-significant

564 **Changes in design for medical devices**

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 a substrate of an immunological test.*	Significant
Change in the design characteristics that allows for additional or broader intended use/indication for 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/indication for 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/effectiveness 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 whether it change its intended performance or not, such as: *All changes in specifications (including shelf life and stability) of an IVD medical device* *Changes in biological or chemical components of reagents*	Significant
Change of the secondary packaging with no impact on storage conditions or stability	Non-significant
Change of colour of the cap of a reagent	Non-significant

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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

569 **Changes to Software for Medical Devices and IVD Medical Devices**

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.* *Changes in the software that modifies the quality controls interpretation or cut off calculation of an IVD*	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.* *Modification of the software to add or remove alarms to monitor the diagnostic procedure on an infectious disease analyzer*	Significant
Change to software that affect the safety and performance/effectiveness 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
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

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
Addition or change of OS version(s) which does not backward compatible. For example: From Windows to iOS.	Significant
Change for compatible with large OS update patch within the same platform. Such as: From Windows X 21H1 to Windows 21H2	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/effectiveness of the device but results in version change and doesn't alter usability of the interface	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/indication for use, principle of operation, and performance/effectiveness	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
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
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

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572 **Changes in materials for 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 non-critical 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

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574 **Changes in materials for IVD medical devices**

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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 changes of reagents of test kits (buffer concentration, addition of preservatives)* *Change in the synthesis/purification methods of biologicals components* *Change from a liquid to solid reagent and vice versa*	Significant
A change in supplier or vendor of the non-critical 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

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577 **Changes to Labelling**

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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 for 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

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