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THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES ON SUBMISSION OF APPLICATION FOR CHANGE(S) TO APPROVED MEDICAL DEVICES AND IN-VITRO DIAGNOSTICS

(*Made under Regulation 23 of the Tanzania Medicines and Medical Devices (Control of Medical Devices Regulations, 2015, GN 315)*

FIRST EDITION

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ABBREVIATIONS

CAB	-	Conformity Assessment Body
DoC	-	Declaration of Conformity
FSCA	-	Field Safety Corrective Action
HSA	-	Health Sciences Authority
IFU	-	Instructions for Use
ISO	-	International Organization for Standardization
IVDDs	-	In-vitro Diagnostics Devices
LRP	-	Local Responsible Person
QMS	-	Quality Management System
SAL	-	Sterility Assurance Level
TMDA	-	Tanzania Medicines and Medical Devices Authority
TMDCA	-	Tanzania Medicines and Medical Devices Act, Cap 219
WHO	-	World Health Organization

ACKNOWLEDGEMENTS

Development of these guidelines was undertaken in order to provide applicants with precise information on documentations and requirements for submitting applications for changes proposed to be made to the medical devices and in vitro diagnostics registered in Tanzania. Such Guidelines were not present before thus making this a first edition.

I would like to express my sincere appreciation to the team of TMDA staff who devoted their time, efforts and contributed successfully in the development of these guidelines. My sincere gratitude are particularly extended to Mr.Sunday Kisoma, Ms. Rehema Mariki, Mr. Bryceson Kibasa, Mr. David Mwakyoma, Ms. Gudula Mpanda, Ms.Jeniva Jasson, Ms. Rose Maingu, Ms. Engerasia Mtui, Ms. Edina Zebedayo, Ms. Marina Sapali, Dr. Shani Maboko and Mr. Edinanth Gareba for their valuable input during development of these guidelines.

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Lastly, I wish to extend a vote of thanks to members of TMDA management for their support and endorsement of these guidelines.

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Acting Director of Medical Devices and Diagnostics Control

FOREWORD

These guidelines are developed as a response to the constraints faced by the applicant during applications for changes made to the approved medical devices and in vitro diagnostics. The guidelines are intended to provide instructions to applicants on how to comply with post approval requirements.

Change on approved medical devices have been categorized based on the risk upon their implementation from significant changes that include Major, Minor, Notifiable and un-permitted changes. Classification of a major change is where the level of risk is considered to be high and is deemed necessary to provide the Authority with adequate time for assessment of the supporting documentation. Minor change is the change that have a potential of lower impact on the function, performance or safety of the approved medical device, notifiable change is the change where there is no impact of safety, quality and performance of approved medical device while un permissible changes are significant changes that may lead to change in the design, performance and intended use of the medical device thus resulting to submission of new application.

TMDA also understand that alternate approaches to the principles and practices described in these guidelines may be acceptable provided they are supported by adequate justification. These approaches should be discussed in advance with the Authority to ensure compliance to regulatory requirements.

As a repercussion to the above, it is equally important to note that the Authority reserves the rights to request information or material, or define conditions not specifically described in these guidelines to allow adequate assessment of safety, quality and performance of approved medical devices and IVDDs.

Applicants are advised to read and follow the requirements outlined in these guidelines. These guidelines should be read in conjunction with other relevant applicable guidance and standards.

Adam M. Fimbo
Director General

DEFINITION OF TERMS

Active Medical Device
Any medical device, operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices.

Active Therapeutic Device
Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness, injury or handicap.

Active Device Intended for Diagnosis
Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or to support in treating physiological conditions, states of health, illnesses or congenital deformities.

Applicant
Means a person who owns a formula or trademark of a product, who may be a manufacturer or a person to whose order and specifications, the product is manufactured and who shall be the marketing authorization holder and have the primary responsibility of the product on the Tanzanian market.

Approved Medical Devices & IVDDs
Means Registered and/ or Notified Medical Devices and IVDDs.

Approved products
Approved Medical Devices & IVDDs

IVDDs Analyser
IVDDs analysers are equipment intended to be used with IVDDs reagents so as to allow the IVDDs reagents to achieve their intended use. IVDDs analysers are typically instruments that analyse the reaction and yield a result of positive, negative, amount of analyte detected, etc.

IVDDs Closed-system analysers
Means instruments that are intended by their product owners to be used with specific reagents, which typically come from the same product owner. Refer to rules of classification of IVDDs in the first schedules of the Medical devices regulations. Risk

classification of the IVDDs analyser will be based on the highest risk class of the intended/compatible IVDDs reagents.

Medical Device or Devices

Means an instrument, apparatus, appliance, material, implement, medical equipment, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component, part of accessory, which is:-

a) Recognized in the official National Formulary, or Pharmacopoeia or any supplement to them;
b) Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals; or
c) Intended to affect the structure or any functions of the body of man or other animals and which does not achieve any of its principal intended purposes through chemical action within the body of man or other animals and which is not depended upon being metabolized for the achievement of any of its principle intended purposes.

Medical Devices with Measuring Function

Device has a measuring function if;

a) The device is intended by the manufacturer to measure: - quantitatively a physiological or anatomical parameter, or - a quantity or a qualifiable characteristic of energy or of substances delivered to or removed from the human body.

b) The result of the measurement - is displayed in legal units or other internationally acceptable units or - is compared to at least one point of reference indicated in legal units or other acceptable units.

c) The intended purpose implies accuracy, claimed explicitly or implicitly, where a non-compliance with the implied accuracy could result in a significant adverse effect on the patient's health and safety.

Medical Device Accessories

Means a separate, finished device intended to "support, supplement, and/or augment the performance" of at least one parent device. Accessories might be marketed individually for use with a specific device type and may be a different class than their parent device.

Medical Device Family

Means a group of medical devices that are made by the same manufacturer that differ only in shape, color, flavor or size, that have the same design and manufacturing process and that have the same intended use.

Medical Device Group

Means a collection of medical devices, such as a procedure pack or tray that is sold under a single name and are supplied in a single packaged unit by the manufacturer of the product. The medical device group comprises of the following:

a) A single proprietary group name;

b) labelled and supplied in a single packaged unit by the product owner; and

c) a common intended purpose.

Medical Device Procedure Pack

Means a medical devices group placed on the market with the purpose of being used for a specific single medical procedure.

Medical Device Spare Parts / Components

Means "any, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." For example, a stethoscope contains multiple parts, including a diaphragm, bell, and tubing. When packaged in whole with the stethoscope, these parts would be considered medical device components that comprise a finished medical device.

Medical Device System

Means a number of components or parts intended to be used together to fulfill some or the entire device's intended functions and that is sold under a single name.

Quality Management System

Means a management system to direct and control an organization with regard to quality, from establishing quality policy, quality objectives and implementing and maintaining quality system.

Recognized Standards

Means national or international standards deemed to offer the presumption of conformity to specific essential principles of safety and performance.

Risk assessment

Means an overall process comprising a risk analysis and a risk evaluation.

Risk

Means combination of the probability of occurrence of harm and the severity of that harm.

Significant Changes

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

a) the manufacturing process, facility or equipment;

b) the manufacturing quality control procedures, including the methods, tests or procedures used to control the quality, purity and sterility of the device or of the materials used in its manufacture;

c) the design of the device, including its performance characteristics, principles of operation and specifications of materials, energy source, software or accessories; and

d) The intended use of the device, including any new or extended use, any addition or deletion of a contra-indication for the device, and any change to the period used to establish its expiry date.

Standalone Analysers
Means instruments that are not intended by their product owners/ Manufacturer to be used with specific reagents. Typically, these instruments can be used with reagents from different product owners/Manufactures.

The product owner does not intend for the analyser to be used with specific reagents; and its labels and user manual do not indicate the performance characteristics of any reagents using the automated protocol of the analyser. Risk classification of any IVDDs analyser will be based on intended use of the IVDDs analyser.

Surgically invasive device
Means an invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.

1. INTRODUCTION

Applicant bares the primary responsibility for quality, safety and performance of medical devices and IVDDs once approved throughout their life cycle. TMDA must establish procedures to ensure that the approved products and manufacturers meet and maintain the established regulatory criteria.

Among other critical functions of TMDA is to evaluate the quality, safety and performance of medical devices and IVDDS. This involves authorizing their use, distribution and sale, which implies granting a market authorization including the changes made once the products have been approved for sale.

Throughout the life cycle of a medical device and IVDDs, the marketing authorization holder (MAH) is responsible for such product that is placed in the market. MAH is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable their product to be manufactured and checked by means of generally accepted scientific methods. Such amendments have to be approved by TMDA prior and or during their implementation.

These guidelines are intended to provide supportive information on the requirements for submission of a change application to implement a change to a Medical Devices and IVDDs. Change applications are categorized into the following; major, minor and notification changes.

The document provides a three-phased assessment tool that includes: general information in identifying a significant change; type of changes, a series of decision trees (appendix 1 – 9) to aid in decision making; and a list of change examples.

2. GENERAL INFORMATION

2.1 Overview

The requirements specified in these guidelines have been adapted from the current WHO Guidance on Reportable Changes to a WHO Prequalified In-vitro Diagnostic Medical Device, Health Canada- Medical Devices Licensing, and Health Sciences Authority (HSA) of Singapore on the details of the various categories of changes to the terms of marketing authorizations for medical devices and IVDDs. These guidelines are intended to provide supportive information on how to present an application to implement a change to an approved+ product.

When changes are considered to be implemented on an approved medical device and IVDDs, these guidelines are to be taken into consideration to assess each change separately, and if application for changes is required, the applicant shall compile supportive evidence in favor of the proposed change and shall describe how the modified device differs from the previously registered device (or device type) in the application form before submitting to TMDA for approval.

During application for change(s), determination of documents to be submitted shall be made through reference to all category of changes from significant changes e.g. major, minor or notification, and or un-permissible change that require new submission for registration or notification. Changes to accessories of approved products will also come within the purview of this document.

Changes that will affect product details in the registration certificate, the applicant should be required to return the old certificate so that the revised certificate can be issued.

2.2 Scope

These guidelines applies to changes of all medical devices and IVDDs products which have been granted market authorization by TMDA through registration or notifications process. Application for changes shall be submitted by the marketing authorization holder or Local Responsible Person (LRP).

2.3 Objectives

2.3. 1 Broad objective;

To provide guidance on application for change(s) made to the approved medical devices and IVDDs.

2.3.2 Specific Objective; -

a) To guide applicants with the classification of changes made to a registered or notified medical devices and IVDDs;

b) To provide guidance on the technical and other general data requirements to support changes to the quality, safety and performance of an approved product.

3. TYPES OF CHANGES

Changes have been categorised into three (3) groups;

a) Major Changes
b) Minor Changes
c) Notifiable Changes

Major Changes or Minor Changes as referred in these guidelines are considered to be significant changes and should be reported to TMDA. A significant change is one that is demonstrated, through risk analysis, having a potential impact on the function, performance, usability, or safety of a registered/notified medical devices and IVDDs. These changes may:

a) Introduce new hazards that have not been previously addressed;

b) adversely affect risks associated with existing hazards; and/or

c) Alter the presentation of existing or new risks to the user (this can involve labelling changes or new indications for use).

Reporting of change should occur prior to its implementation. Applicants should submit applications early in the process of designing and validating the change, to allow sufficient time for assessment by the Authority before its approval. Notifiable changes are changes that manufacturer may implement them and notifies the Authority immediately.

3.1 Major changes

These are the significant changes that have been confirmed through risk analysis, to have a potential higher impact on the function, performance, usability, or safety of the approved medical devices or IVDDs. Change may affects either product's safety, quality, performance or both. These changes should not be implemented in unless they have official approval from the Authority.

A letter of acceptance will be issued for all major changes when the proposed change is considered acceptable.

3.2 Minor changes

These are the significant changes that have been confirmed through risk analysis, to have a potential of lower impact on the function, performance, usability, or safety of the approved product.

Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the application for change.

Such changes can be implemented if the Authority has not issued objection letter within **10** days from the date of acknowledgement of receipt. Should queries arise during the specified period; then the change can only be implemented on receipt of a letter of acceptance from the Authority.

3.3 Notifiable changes

These are type of changes whose implementation has no impact to the product safety, quality and performance. They may be implemented by the manufacturer without prior approval from the Authority, but should be reported upon completion of their implementation, as a notification.

The following specified change(s) are considered to be notifiable changes;

a) Labelling changes that only involve changes in layout, colour, font sizes and design, without change in prominence of precautions, warnings and contraindications.
b) Labelling changes that involve the addition and/or removal of languages not required by the Authority.
c) Labelling changes that involve the addition/removal of reference agency approvals (e.g. CE Marking).
d) Labelling changes that involve the update of distributor information, including EU authorised representative, and which does not affect the device approved information.
e) Labelling changes that involve the addition/change or removal of barcodes, and which does not change the device registered information.
f) Labelling changes that involve the addition of a Unique Device Identifier (UDI), and which does not change the device approved information.
g) Labelling changes that involve the change in date format of an existing labelling date field (e.g. from MMYY to DDMMYY).
h) Change in regulatory status on rejection or withdrawal in any reference agencies for models registered on medical devices register.
i) Raw material supplier changes (except medicinal substances and biological material suppliers) that do not change the registered medical device or IVDDs specifications.

j) Change in scope of the quality management system (QMS) certification which does not affect the registered medical device.
k) Change in certification body with no change in scope of QMS certificate.

4. UN-PERMISSIBLE CHANGES

The following changes do not qualify to be applied as changes of the approved product. The manufacturer should consider to file a new application for approval instead:

a) Change that will results in the changes in risk classification of the approved medical devices or IVDDs.

b) Change to the specific disorder, condition or risk factor of interest that the IVDDs is intended to detect, define or differentiate.

c) Change in approved intended use of the medical devices or IVDDs.

d) Change to what is detected (i.e. the analyte or measurand).

e) Changes in antigens, antibodies, primers or solid phase of the IVDDs.

f) Change of the drug substance combined with the registered medical device.

g) Change of the registrable drug of a device with the registrable drug in a secondary role.

h) Addition of model that does not fulfil the grouping criteria as per i.e Medical devices or IVDDs Family/ Procedure Kit/ Group definitions.

i) Addition of medical devices with device brand names different from the registered medical devices or IVDDs.

j) Change in the test result format from qualitative to quantitative or vice versa.

k) Change in biological or chemical principle of the test.

l) Change in design of test technology.
m) Combination of several changes can also result in the need for a new registration application.

Other combination of multiple changes could lead to the proposed changes to fall in the categories of the Un-permissible changes. Therefore, applicants are advised to use these guidelines while categorising their changes in conjunction with guidance from TMDA.

5. CHANGE TYPE ASSESSMENT DECISION TREES

The decision trees detailed in this section present guiding principles for identification of the category of change applicable for each proposed type of change to the approved product.

The “Main Decision Tree” shall be used to determine the applicable decision for a specific change. Examples of changes are included in the decision trees for ease of reference. Please note that the examples are not meant as an exhaustive list.

5.1 Main Decision Tree

This decision tree describes the general types of changes that can be made to a medical device and IVDDs. It leads the applicant to more detailed information contained in Decision Trees A to H (Appendix 1 – 9).

Applicants are advised to proceed through the entire flow, and identify all relevant changes impacting the approved products and information which were provided in initial submission.

5.2 Decision Tree A - Changes to Manufacturing Processes, Facility or Equipment

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

In cases where the manufacturer's name and address on the device labelling stays the same but a new manufacturing facility is added, the new facility will need to be covered by the manufacturer's quality management system certification. The manufacturer is also required to submit a registration certificate for a change in manufacturer’s name or address. A signed and stamped attestation letter, declaring the manufacturing specifications to be the same in the new manufacturing facility, has to be added in the submission. If the manufacturer makes this attestation, an amended registration certificate may be issued without further evidence of safety and effectiveness.

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

Changes in sterilization procedures are often considered to be significant. Please refer to Section 5.5 on Sterilization and Decision Tree D for clarification.

5.3 Decision Tree B - Changes to the Manufacturing Quality Control Procedures

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

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

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

5.4 Decision Tree C - Changes in Design

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

5.4.1 Control Mechanism

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

5.4.2 Operating Principles

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

5.4.3 Design Specifications

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

If the response to any of the following three questions is yes, then it is likely that the design change is significant and an application for changes is required.

a) Does the design change affect the indications for use?

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

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

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

5.5 Decision Tree D - Changes to Sterilization

The nature of sterilization is such that it is impossible to determine by inspection and testing if the sterilization of the actual device(s) has been successful. Medical devices are considered sterile if manufacturers can demonstrate a sterility assurance level (SAL) of 10^{-6} or better. The sterilization process needs to be verified and validated and its performance routinely monitored.

For this reason, the TMDA requires documentation pertaining to changes in sterilization method or process for medical devices or to any changes that might affect the effectiveness of the process.

Such changes include:

a) Changes that increase the bioburden alert or action levels or that introduces an organism that is more difficult to kill,

b) device design and material changes that introduce a feature that is more difficult to sterilize;

c) changes in sterilization process or equipment or cycle parameters;

d) changes in the density or configuration of the sterilization load;

e) changes to the quality control verification and validation process such as introducing parametric release.

This rationale also applies to changes in the packaging of medical devices subject to sterilization. In general, any change to the sterilization method or process of a medical device, or a change to the packaging for the sterilization of a medical device is considered to be a significant change.

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

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

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

5.6 Decision Tree E - Changes to Software

Many changes to a device's software will require application for changes.
The following would be considered significant changes:

a) a software change, which impacts the control of the device, that may alter the diagnosis or therapy delivered to the patient;

b) a change in software that modifies an algorithm impacting the diagnosis or therapy delivered;

c) a software change that impacts the way data is read or interpreted by the user, such that the treatment or diagnosis of the patient may be altered when compared to the previous version of the software;

d) a software change that replaces previously required user input a closed loop decision;

e) addition of a new feature to the software that may change the diagnosis or therapy delivered to the patient;

f) introduction to or removal of a new alarm function from the software such that a response to the new configuration may change the treatment of the patient in comparison to the previous version of the software;

g) a software change that incorporates a change to the operating system on which the software runs.

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

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

The following would not be considered significant changes:

a) a software change that only introduces non-therapeutic and/or non-diagnostic features such as printing, faxing, improved image clarity, reporting format or additional language support;

b) a software change that only modifies the appearance of the user interface with negligible risk of impacting the diagnosis or therapy delivered to the patient;

c) a software change that disables a feature that does not interact with other features

5.7 Decision Tree F - Changes in Materials for non in vitro diagnostic devices (IVDDs)

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

a) All changes to the sourcing or processing of materials of human or animal origin are considered significant and result in application for change approval.

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

In each of the above instances, it must be determined if the device is a surgically invasive device intended to be absorbed by the body or to remain in the body for at least thirty consecutive days.

If this is the case, and the changed material would be in contact with body tissues or fluids, then and application for changes is required. Even when the material would not be in contact with body tissues and fluids, the question of design specifications arises. If changes to the design specifications are required, they should be reviewed with the guidance of Decision Tree C.

If the supplier or vendor of the material changes, but the material meets the manufacturer's previously approved acceptance criteria, with the exception of human or animal derived materials, then that change is minor change.

5.8 Decision Tree G - Changes in Materials in in vitro diagnostic devices (IVDDs)

There is a distinction between IVDDs and other devices with regard to material changes. This section also considers changes to the method used to perform an approved test.
Changes to materials in an IVDD often affect its performance characteristics, including specificity or sensitivity, and would be assessed as to their impact on the safety and effectiveness of the device.

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

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

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

5.9 Decision Tree H - Changes to Labelling

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

Changes to the intended use or indications for use will require a new application unless the changes are within an approved set of indications. Changes within an approved set

of indications should be submitted at the renewal or as a change notification. However, if a limitation to the indications for use is introduced as a result of concerns associated with the safe and effective use of the device, a contraindication must be added. This is considered a significant change.

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

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

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

Changes to labelling to include additional languages required in other regulatory jurisdictions are minor changes.

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

Generally, a change in the shelf life of a non IVDD in Class A and Class B may be categorized as minor changes. However, if the protocols and methods for determining shelf life have been changed or have not been reviewed in a previous application, then is a major change where the Authority approval is required.

6. APPLICATION PROCESS FOR CHANGE(S)

Upon identifying all applicable categories of changes based on the decision trees in Section 5.0, the changes may be grouped as per guidelines below, and submitted as a single Change application for the approved medical device or IVDDs.

6.1 Type of Change Application Submission

The following should be considered while the applicant applies for approval of the changes for the approved devices;

6.1.1 Application of Multiple Changes within one approved product:

Multiple changes i.e Major, Minor and Notification, will be considered in one Change application if they are submitted together. Fees and assessment done will follow the highest change category in that application.

6.1.2 Application of Identical changes affecting Multiple Approved Products:

a) Applicants can submit one application for changes to TMDA for:

(i) identical administrative changes to multiple approved products,
or

(ii) Where the same new product is added to multiple approved products, only if the changes are submitted together.

Non-identical changes in any one listing may result in the entire application for changes being unaccepted.

b) Applicants can submit one application for change in to the same medical device that is part of multiple device registration (as part of a Family, System, Group, Test Kit). Product selected for implementation for the proposed changes must be the same in the registered family, system, group, or test kit.

c) Non-identical changes that do not fall under the categories above: Applicant should submit separate application for each change to TMDA.

6.1.3 Application for changes involving devices registered in different risk classes

Identical changes involving Registered Medical Devices of different risk classes may be submitted in one application for change only for the following categories of changes**.**

a) Change in product Applicant/Market Authorization Holder.

b) Change in manufacture and/or sterilization site.

c) Change only involves an update of QMS certificate validity date.

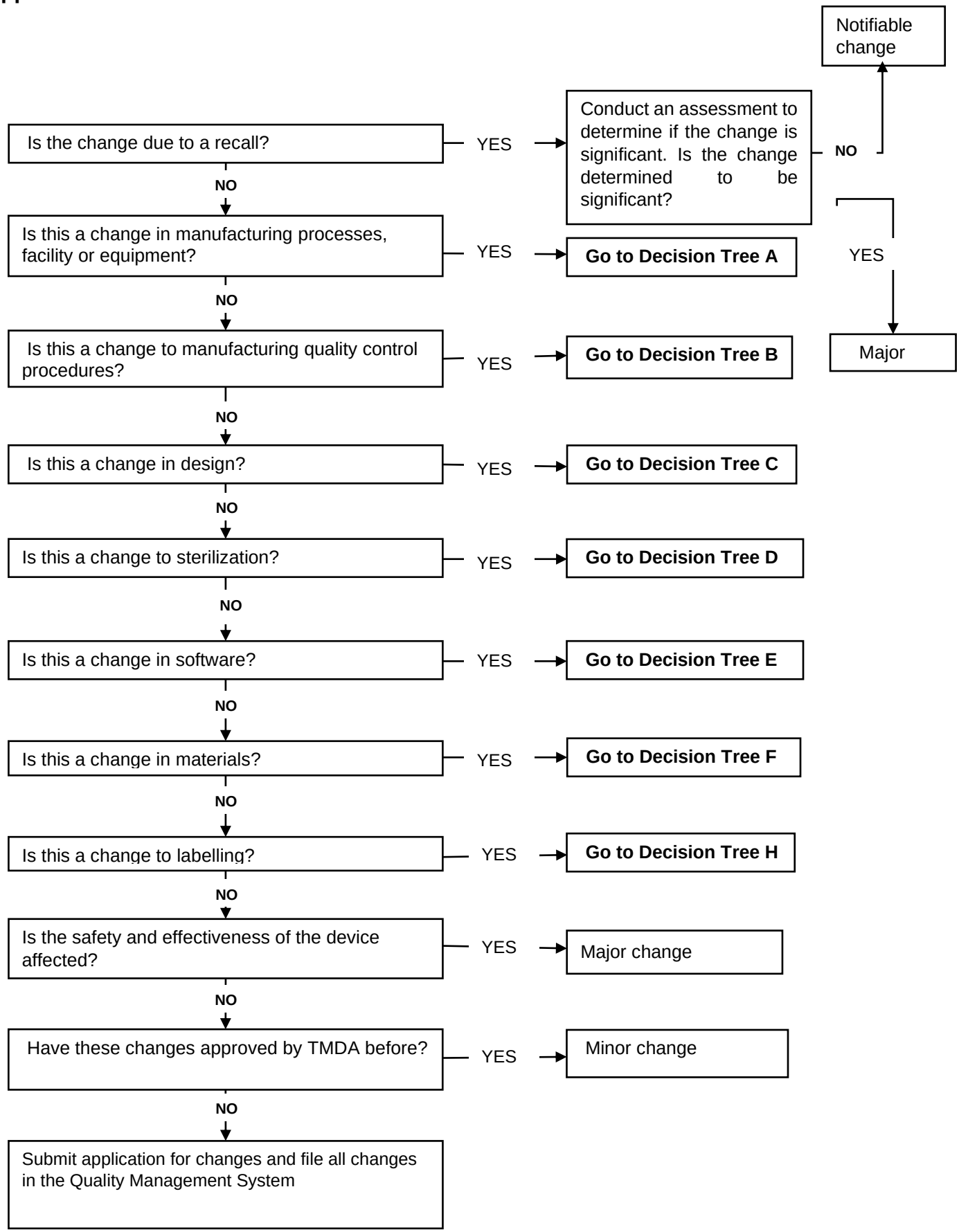
d) Addition of identical Class A accessories.

6.2 Changes Triggered by Recall

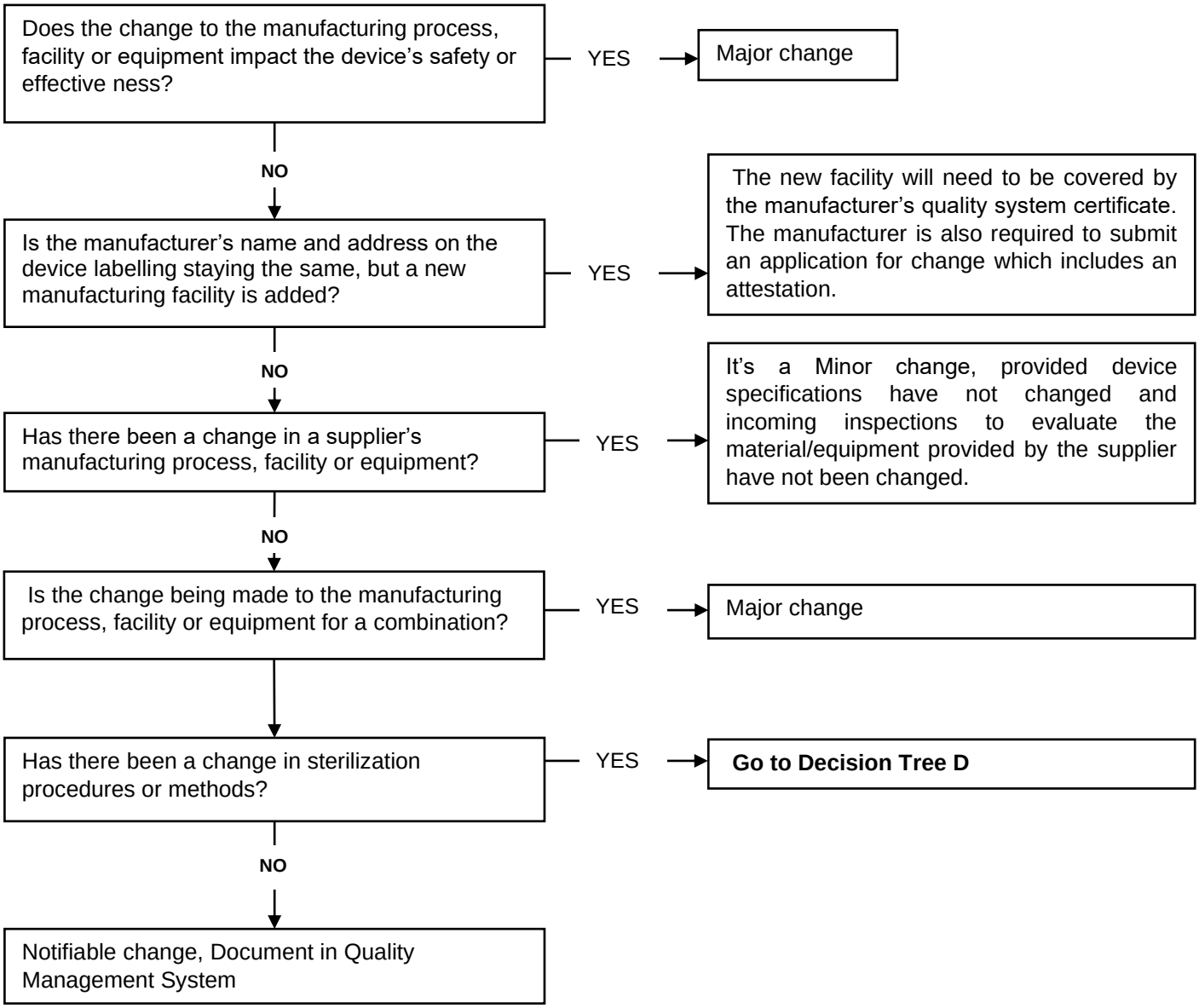
Changes occurring as a result of a recall are to be assessed to determine if they are significant, including design changes or design specification changes required to bring a medical device back in line with previous performance specifications. Cover letters accompanying device applications in response to a recall should clearly identify that the application for change is being submitted for this purpose.

Applicant should contact TMDA directly before submission of application for change if nature of the product changes is associated with recalls. Following a recall, the review time of these changes applications will be determined in consideration of both the nature of the changes involved and any potential safety concerns.

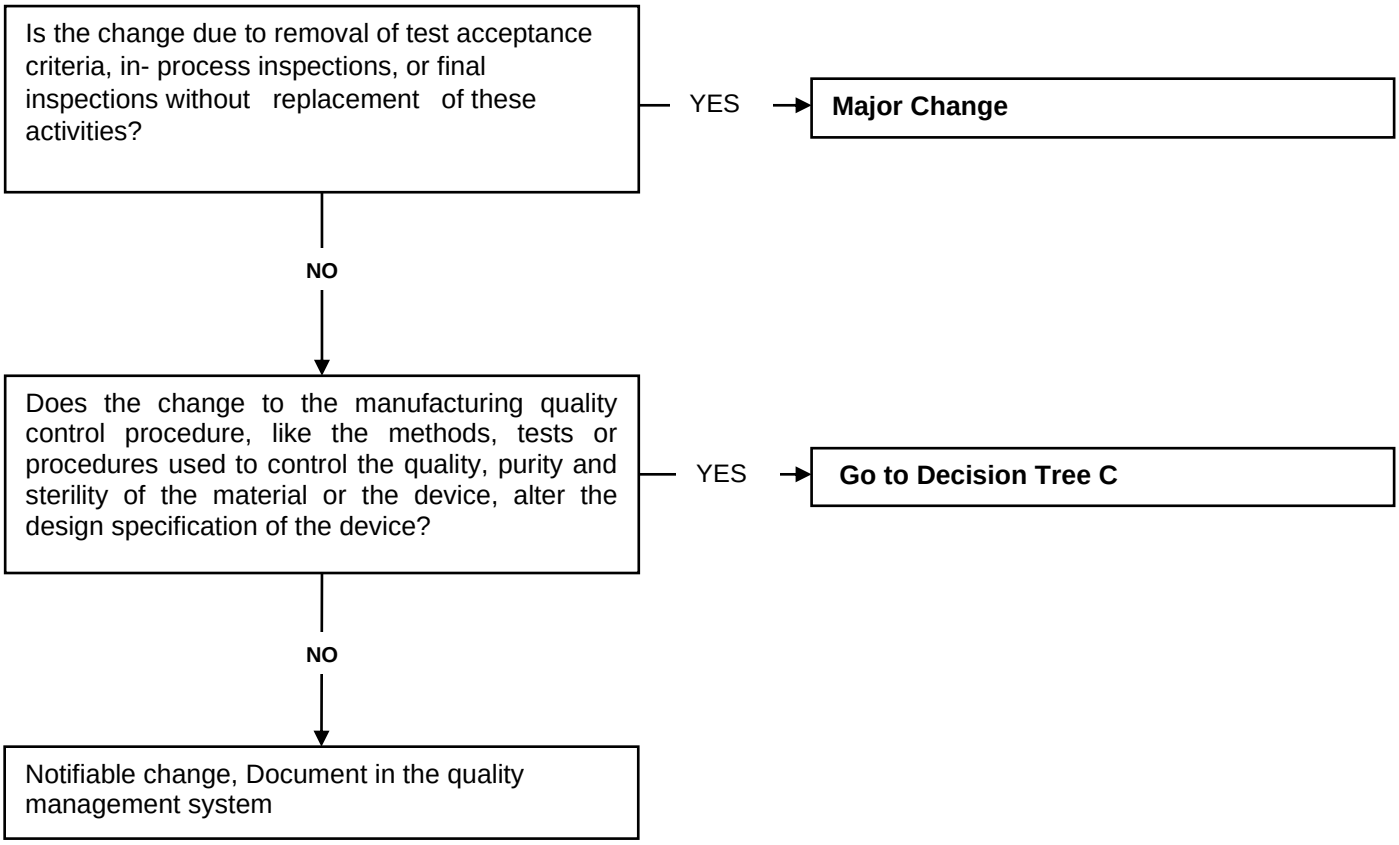
Appendix 1: Main Decision Tree



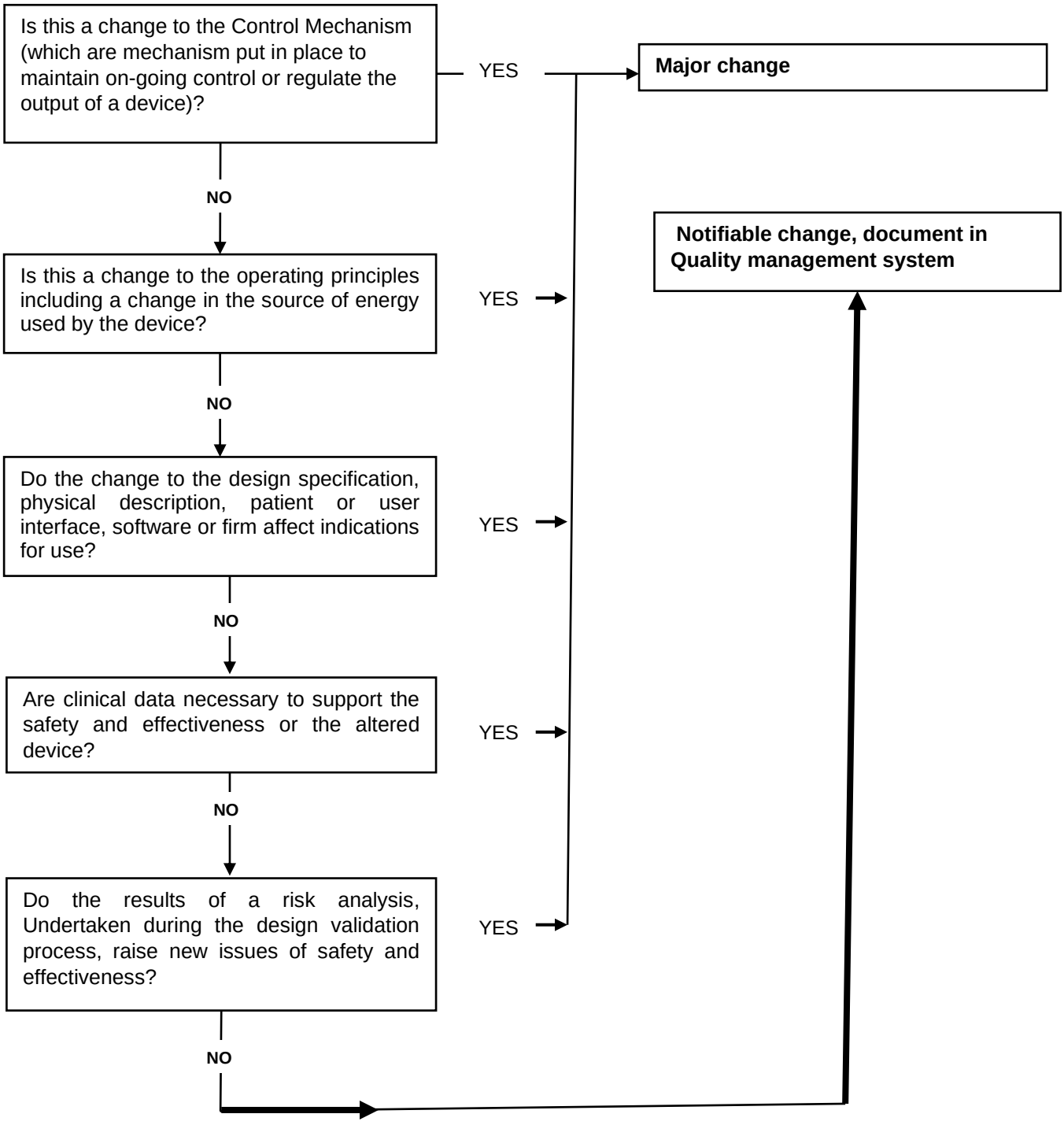
Appendix 2 – Decision Tree A: Changes to Manufacturing Process, Facility or Equipment



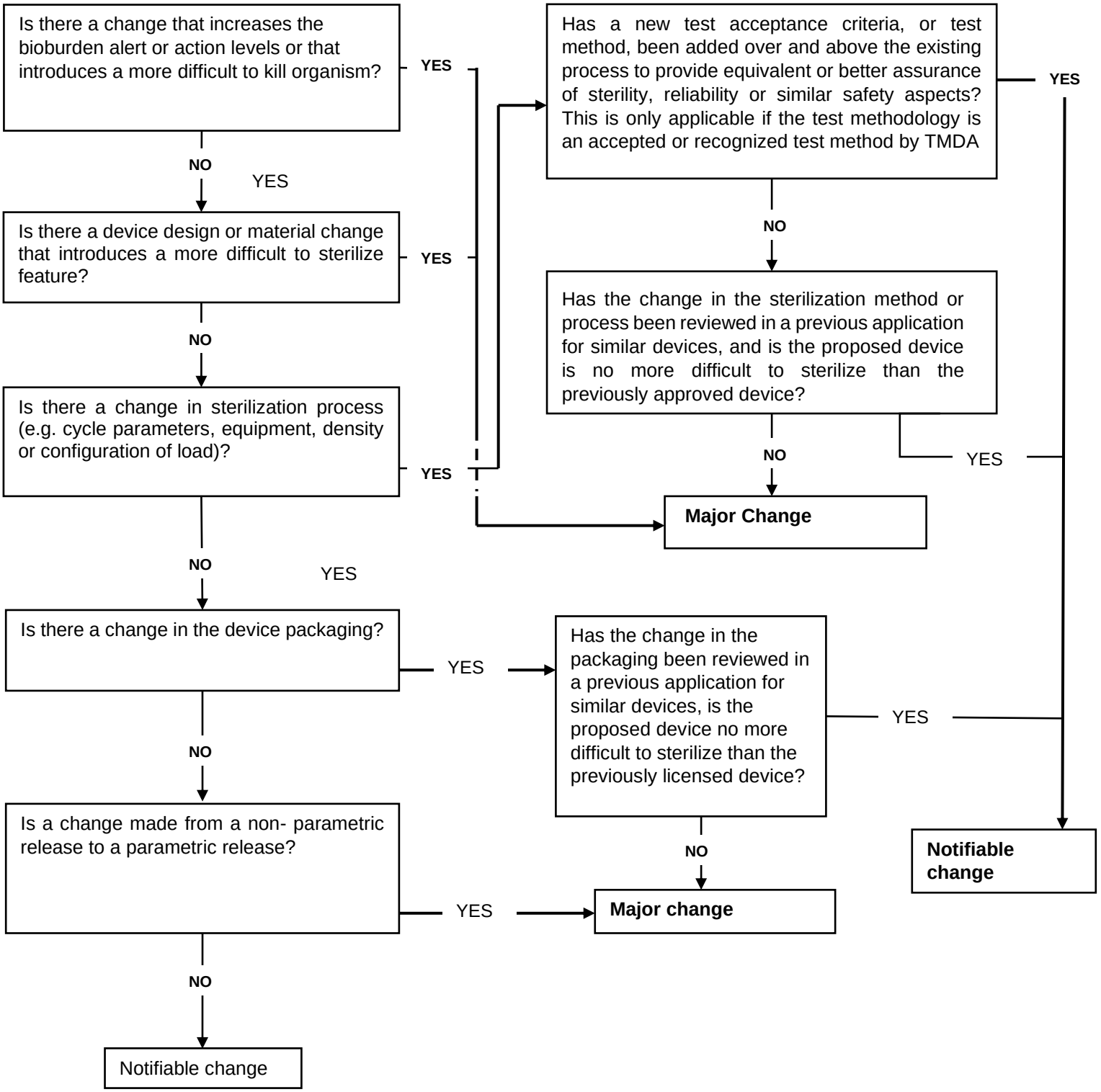
Appendix 3 - Decision Tree B: Changes in Manufacturing Control Procedures



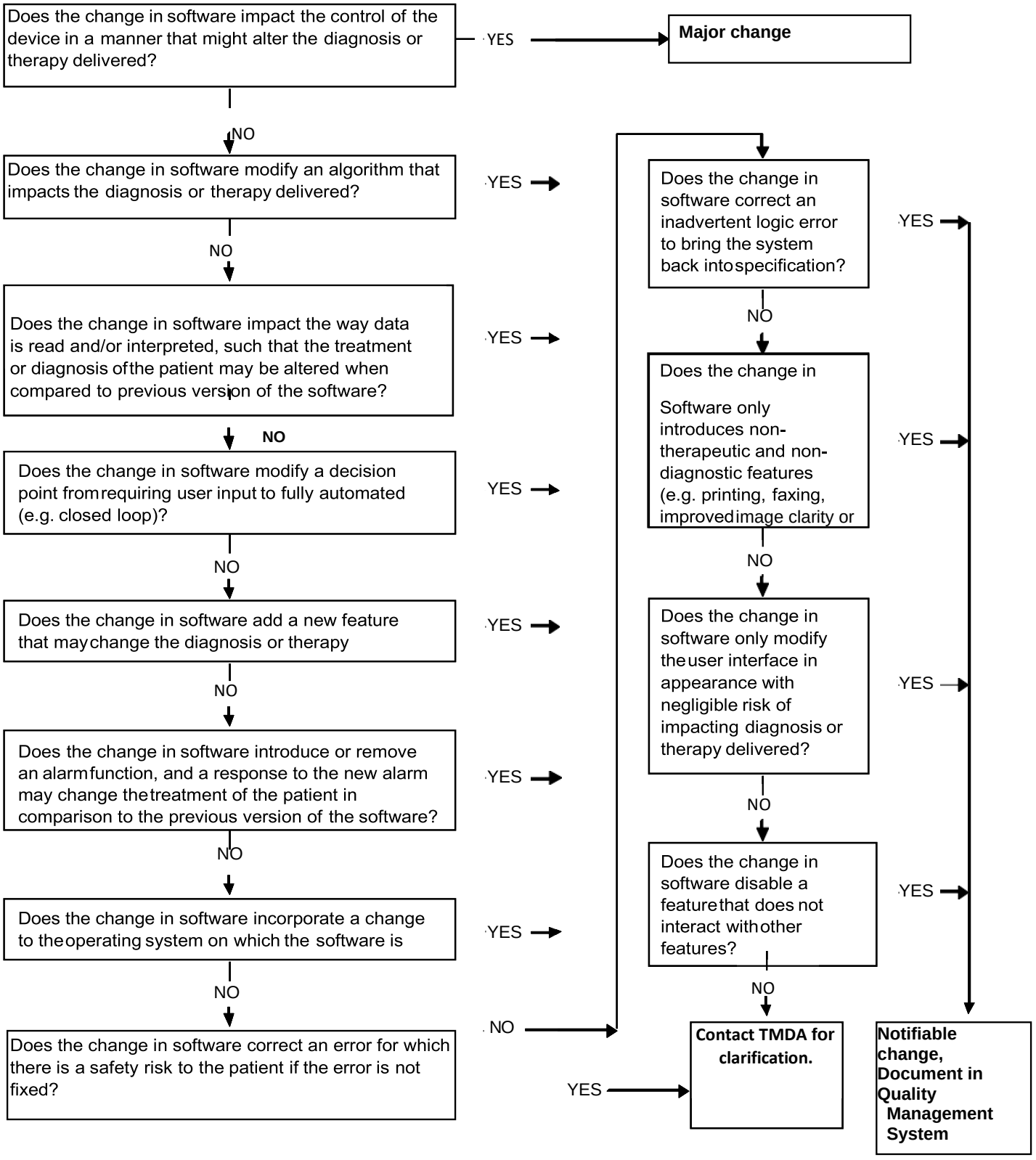
Appendix 4 - Decision Tree C: Changes in Design



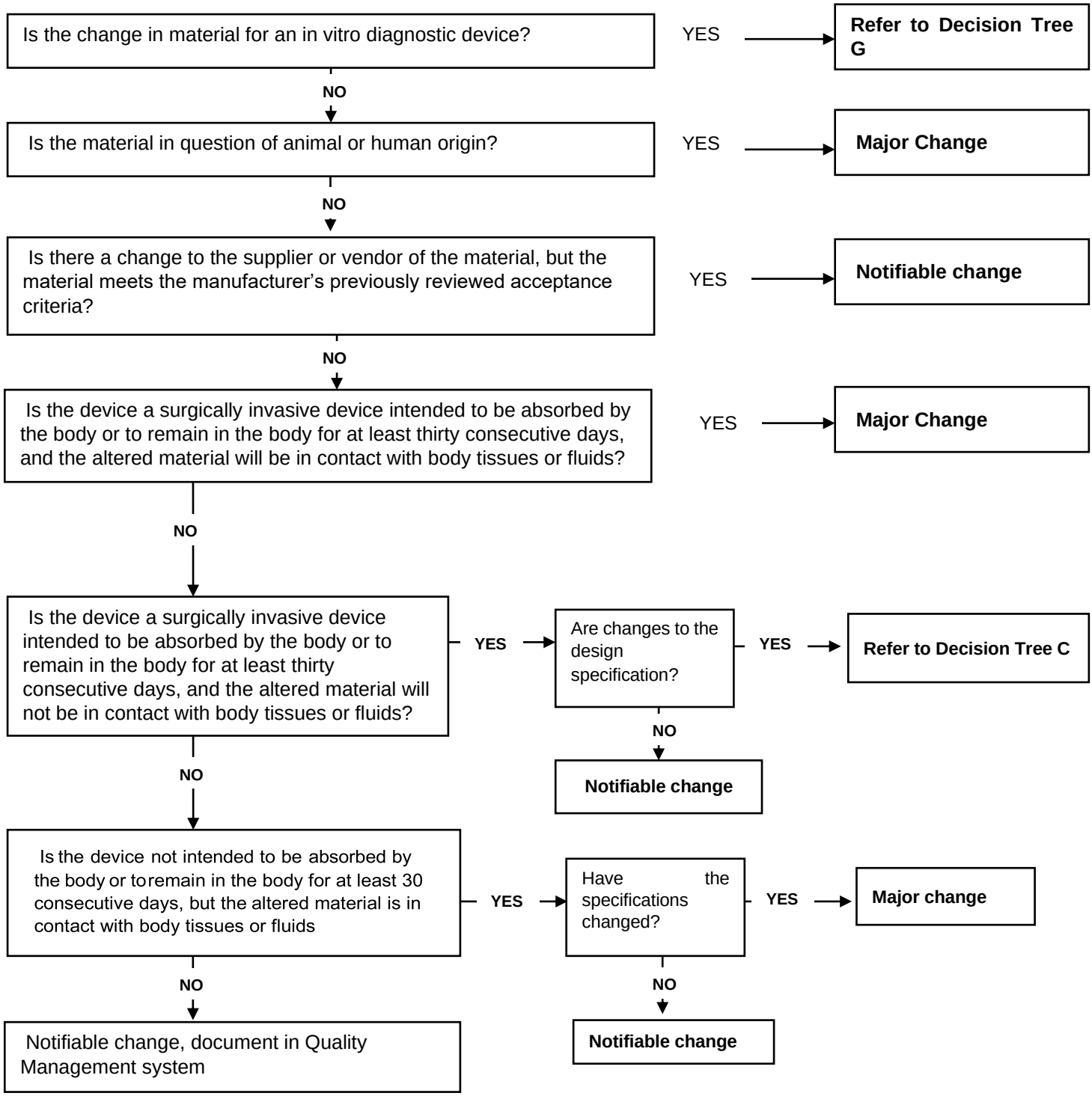
Appendix 5 - Decision Tree D: Sterilization of Medical Devices



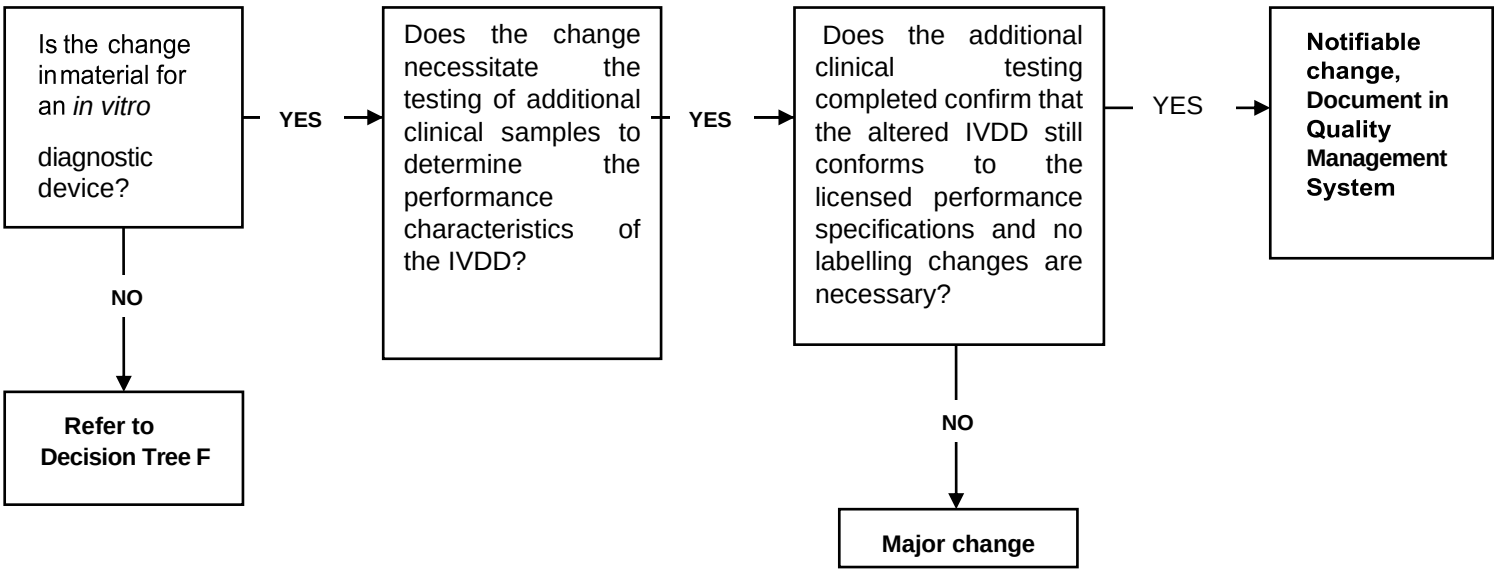
Appendix 6 – Decision Tree E: Changes to Software



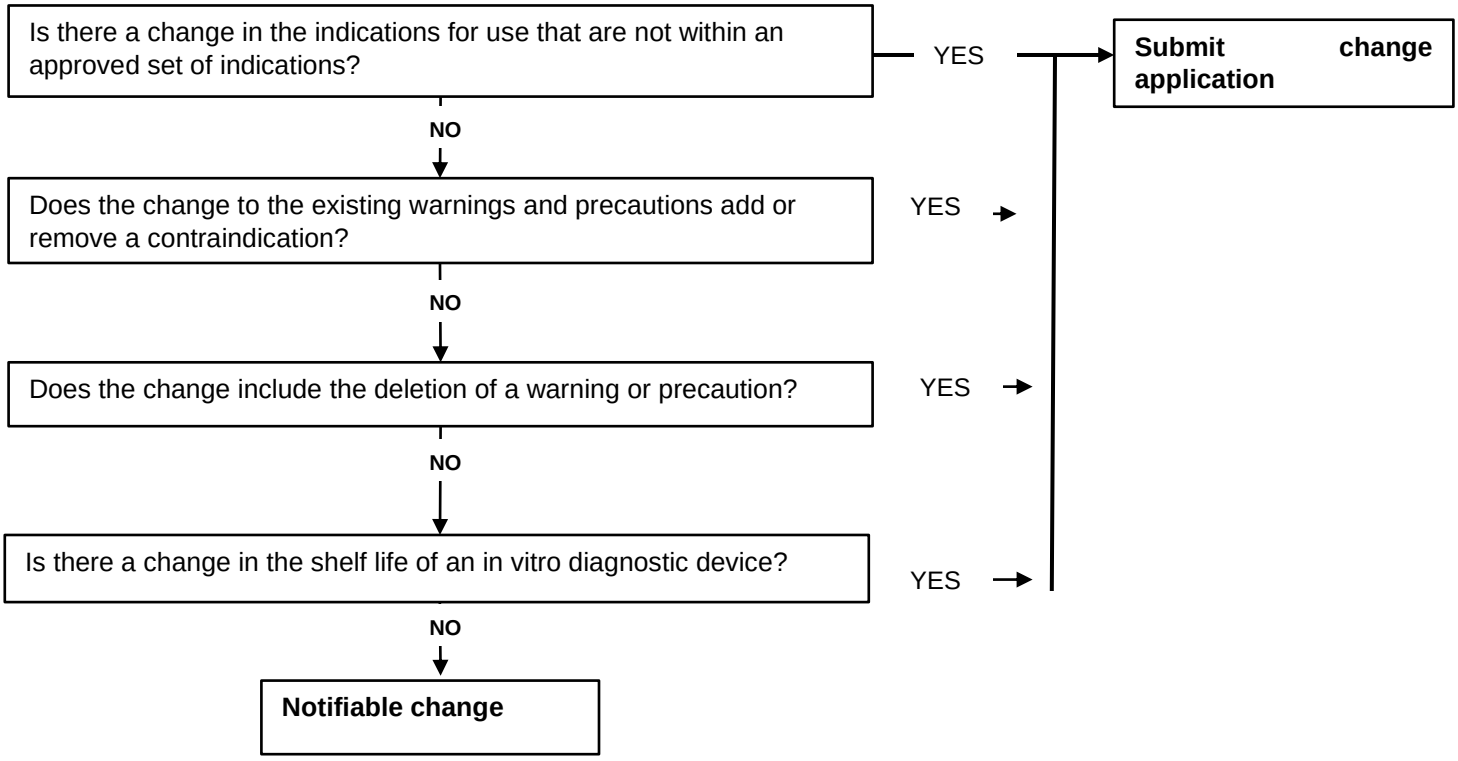
Appendix 7 - Decision Tree F: Changes in Materials for non-IVDDs



Changes in Materials for IVDDs



Appendix 8 – Decision Tree H: Changes to Labelling



Appendix 9 - Changes Documentation

Documentary Requirements	**Change in Manufacturing Facility, Process and Quality Management System (QMS)**				
	All changes in manufacturing and/or sterilisation facilities with no changes to the specifications of a registered medical device and/or sterilisation process	All changes in manufacturing process to Additive Manufacturing, or to refurbish a registered device	All changes in the manufacturing site and/or processes that result in a change in specifications of a registered medical device	All changes in sterilisation method and/or related processes for a registered medical device	Update of QMS certificate validity date
Proof of QMS – E.g.: ISO 13485 Certificate, Conformity to US FDA Quality System Regulations or Japan MHLW Ordinance 169	✓	If applicable	If applicable	✓	✓
Device labelling with changes are highlighted/identified and finalised device labelling	✓	If applicable	If applicable	✓	If applicable
Declaration from product owner on company letterhead to state that there is no change to device in all aspects, including intended use, technical specifications and/or sterilisation process	✓				
Sterilisation validation report (including EO residuals report if applicable) and evidence of on-going sterilisation validation.	If applicable			✓	
Summary of new manufacturing process		✓	✓		
Design verification and validation documents		✓	✓	post-sterilisation functional test report	
Risk Analysis (If applicable)		✓	✓		

** For changes in manufacturing/ sterilisation site of medical devices containing medicinal products in an ancillary role, please contact the TMDA for further advice.*

Documentary Requirements	**Changes in Design or Specifications of a approved medical devices and IVDDs**		
	Changes to the control mechanisms, operating principles, sterile primary packaging and/or design characteristics of a registered medical device**.**	Unless the change only involves a change to the software version number such as: • Software changes solely to correct an inadvertent software error which does not add new functions, does not pose any safety risk and is intended to bring the system to specification; • Software changes which augment interfacing to other nonmedical peripherals such as printers or VDUs and which has no diagnostic or therapeutic function; • Software changes which only modifies the appearance of the user interface with no risk to diagnostic or therapeutic function of the device. Software changes solely to address a cybersecurity vulnerability	All changes in specifications of a registered medical device (including shelf life, stability, expiry date)
Design verification and validation documents * Refer to Documentation Guidelines for Software Changes table in this Annex	✓	✓	✓
Risk Analysis	✓		✓
Clinical Evidence (If applicable)	✓		✓
Device labelling with changes are highlighted/identified and finalised device labelling	✓	✓	✓

Documentation Guidelines for Software Changes

	Software change (Notification)	**Software change (Technical/ Review)**
Detailed summary of software changes (can be included in the Annex 2, Summary Table of Change). To include information on the incremental changes or revisions to the software from the registered software version. To provide the final software version to be supplied in Singapore. Note: The final software version that represents all software changes/iteration (e.g. graphic interface, functionality, bug fixes and etc.) should be provided. Software version numbering that is solely for testing or internal use only (e.g. checking in of source code) are not required.	✓	✓
An overview of all verification, validation, and testing performed for the software both in-house and in a simulated or actual user environment prior to final release.		✓
All unresolved anomalies in the release version of the software should be summarized, along with a justification for acceptability (i.e. the problem, impact on safety and effectiveness, and any plans for correction of the problems).		✓
Evidence to demonstrate that the software issue has been resolved.		✓ (e.g. test cases verification)

Note- for in vitro diagnostic (IVD) devices, performance validation of the IVD analyser & assay conducted using software is acceptable in lieu of the software validation report.

Documentary Requirements	Changes to Materials in a General Medical Device				
	All changes to 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.	All changes to material or material formulation (of non-biological origin) including changes to device coating or surface modification techniques that is intended to make direct/indirect contact with body tissues and fluids or is absorbed by the body, with no change in device performance specifications.	Unless the material has been reviewed in a previous device application and the new material has the same nature of body contact and contact duration.	All changes to materials that are used for shielding in medical devices emitting ionising radiation.	All changes to concentration or drug specification of medicinal substances in medical devices that incorporate medicinal substances in an ancillary role.
Design verification and validation documents	✓ (e.g. biocompatibility)	✓ (e.g. biocompatibility, mechanical)	✓ (e.g. biocompatibility, mechanical testing, sterilisation validation)	✓ (e.g. radiation safety validation report summary)	Contact TMDA for further advice.
Clinical Evidence (If applicable)	✓	✓		✓	
Biological safety data - Process validation results to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents. This also includes inactivation of infection organisms.	✓ (e.g. viral validation report)				
Information of sources/donors -An indication of biological material or derivative used in the medical device, its origin and source/donor	✓				

Documentary Requirements	Changes to Materials in a General Medical Device				
	All changes to 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.	All changes to material or material formulation (of non-biological origin) including changes to device coating or surface modification techniques that is intended to make direct/indirect contact with body tissues and fluids or is absorbed by the body, with no change in device performance specifications.	Unless the material has been reviewed in a previous device application and the new material has the same nature of body contact and contact duration.	All changes to materials that are used for shielding in medical devices emitting ionising radiation.	All changes to concentration or drug specification of medicinal substances in medical devices that incorporate medicinal substances in an ancillary role.
List of material(s) making direct/ indirect contact with human body	✓	✓	✓		
Information on radiation source				✓	
Information on materials for shielding of radiation				✓	
Justification for choice of identified referenced device (provide device registration & model number), with consideration to the device intended use, indications of use, nature of body contact and contact duration.			✓		

Documentary Requirements:	Change to Materials of In Vitro Diagnostic Medical Devices
	All changes to material (including chemical and biological substances) which results in a change to the performance specifications of the registered in vitro diagnostic (IVD) medical device
Design verification and validation documents	✓ e.g. Shelf life studies, specificity and sensitivity studies
Clinical Evidence	✓
Biological safety data - Process validation results to substantiate that manufacturing procedures are in place to minimize biological risks, in particular, with regard to viruses and other transmissible agents. This also includes inactivation of infection organisms in reagents and the production of reagents.	✓ *e.g. Certificate of Analysis (COA), Certificate of Compliance (COC)*
Information of sources/ donors -An indication of biological material or derivative used in the medical device, its origin and source/donor	✓
Device labelling with changes are highlighted/identified and finalised device labelling	
Risk analysis	

All changes to the radiation source require a new premarket submission. E.g. Radioisotopes in radioimmunoassays

Documentary Requirements	**Changes to Labelling**						
	All changes to the labelling of medical devices that involve addition and/or revision of the approved indications for use	Unless the change only involves a reduction of indications for use	All changes to labelling of the medical devices that involve removal and/or revision of warnings, precautions and/or contraindications	Unless the change involve an addition of contraindications, warnings and/or precautions	Labelling changes that modify the approved method of use OR Involves a change from 'professional use only' to 'home use'	Change involves only rephrasing of existing information in instructions for use	Other labelling Changes
Proof of reference agency's approval(s) for the change	✓						
Device labelling with changes that are highlighted/identified and finalised device labelling	✓	✓	✓	✓	✓	✓	✓
Declaration of conformity document	✓						
Device verification and validation documents *Refer to Documentation Guidelines for Software Changes table in this Annex	✓		✓		✓		
Clinical Evidence	✓		✓				
Risk Analysis	✓		✓	✓	✓		
Other relevant documents supporting proposed							✓

changes submitted (If applicable)							

Documentary Requirements	**Changes to registered medical devices approved information**							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
Annex 2 - List of Configurations with new/ updated models highlighted	✓	✓	✓	✓	✓	✓		
Device description of the added model	✓	✓	✓	✓				
A comparison, preferably in a table, of the design, specifications, intended use/indications for use between the current registered	✓	✓	✓	✓	✓ Justification for deletion of model(s)			

Documentary Requirements	Changes to registered medical devices approved information							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
devices and the proposed added device(s) the proposed. To include labelled pictorial representation (diagrams, photos, drawings) where necessary.								
Justification for addition of device models to be grouped within the registered listing [e.g. Patient information leaflet and promotional material (including	✓	✓	✓	✓	✓ Justification for deletion of model(s)			

Documentary Requirements	Changes to registered medical devices approved information							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
brochures and catalogues)]								
Cybersecurity (if applicable) Evidence to support the cybersecurity of connected medical devices, such as wireless enabled, internet-connected and network-connected devices. For example, but not limited to:	✓	✓	✓					

Documentary Requirements	**Changes to registered medical devices approved information**							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
-Cybersecurity vulnerabilities and risk analysis -Cybersecurity control measures -On-going plans, processes or mechanisms for surveillance, timely detection and management of cybersecurity related threats during the useful life of the device especially when a breach has been detected.								

Documentary Requirements	Changes to registered medical devices approved information							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
Device labelling with changes are highlighted/ identified and finalised device labelling	✓	✓	✓			✓	✓	✓
Declaration of conformity document	✓	✓	✓			✓	✓	
Letter of Authorisation	✓	✓	✓	✓		✓	✓	✓
Device verification and validation documents *Refer to Documentation Guidelines for Software Changes table in this Annex	✓	If applicable	If applicable					

Documentary Requirements	Changes to registered medical devices approved information							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
Clinical Evidence (If applicable)	✓							
Risk analysis (If applicable)	✓							
Proof of reference agency's approval(s) for the change	✓							
Marketing History* (List of countries where the medical device is marketed. Date (accurate to MMYYYY) and country where the device was first introduced for	✓	✓	✓	✓				

Documentary Requirements	Changes to registered medical devices approved information							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
commercial distribution globally.)								
Adverse events (AE) / Field safety corrective action (FSCA). - To include a summary of reportable AEs and FSCAs for the MD since its first introduction on the global market. If there have been no AEs or FSCAs to date, provide an attestation from product owner on	✓	✓	✓					

Documentary Requirements	Changes to registered medical devices approved information							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
company letterhead, that there have been no AEs or FSCAs since commercial introduction of the device globally.								
Manufacturing information (site's name and address)	✓	✓	✓	✓				
Proof of QMS – E.g.: ISO13485 Certificate, Conformity to US FDA Quality System Regulations or Japan MHLW Ordinance 169	✓	✓	✓	From Registrant on company letterhead, to state (1) The added models are		From product owner on company letterhead, to state that there is no change to the device in all	From product owner on company letterhead, to state that they will undertake responsibility	

Documentary Requirements	**Changes to registered medical devices approved information**							
	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	
				Class A devices; (2) Class A device name and identifier; (3) The name of product owner; (4) Name and address of manufacturing site(s) for the Class A devices		aspects, including intended use, technical specifications and/or sterilisation process.	to provide post market support and assistance related to the medical devices <state device name> already supplied under the former product owner's name (if applicable)	
Declaration Letter								

	Changes to registered medical devices approved information							
Documentary Requirements	Addition of new medical devices to medical devices register	Unless the change involves the addition of the same design, that only involves: • New models within the existing range of sizes already registered; • An increase or reduction in the number of identical devices in a pack of a registered device without breach of individual primary packaging; • An increase or reduction of volume that does not affect specifications of device (e.g. shelf life, stability, performance and sterility); Addition of models due repackaging of existing models within the same SMDR listing in different combinations without breach of individual primary packaging.	Unless change involves the addition of a new device or software identifier with no change to the performance characteristics or specifications of the device	Unless the change involves the addition of Class A medical device accessories that complement the registered medical device as a closed system	All deletions of models from device listing	All changes to Product Name and/or identifier	All changes to the product owner	

Bibliography

1. The Tanzania Medicines and Medical Devices (Control of Medical Devices) Regulations, 2015
2. Guidelines on Submission of Documentation for Registration of Medical Devices, 3rd Edition, April 2020
3. Guidelines on Submission of Documentation for Registration of In Vitro Diagnostics Devices, 3rd Edition, April 2020
4. Change Notification applications arising from the EU MDR/IVDR related changes to registered medical devices, 6th November, 2020
5. GN-21: Guidance on Change Notification for Registered Medical Devices Revision 4.7, February 2020 (HSA)
6. GN-24: Guidance on the change of Registrant, Revision 1.3 August 2018
7. GN-25: Guidance on the Cancellation of Medical Device Listing Revision 1, December 2017
8. GN-34: Guidance Document for IVD Analysers Revision 1.3, February 2020
9. Reportable Changes to a WHO Prequalified In Vitro Diagnostic, Draft for public comment 10 February 2016
10. Guidance for the Interpretation of Significant Change of a Medical Device, January 20, 2011, Health Canada
11. Variation Guideline, Food and Drug Administration, July 2012
12. Reportable Changes to a WHO Prequalified In Vitro Diagnostic Medical Device, December 2016
13. Overview of the WHO Prequalification of In Vitro Diagnostics Assessment, 2018
14. Prequalification Assessment and Change Assessment Target Deadlines, Prequalification of In Vitro Diagnostics, July 2017