The European Association
Medical Devices - Notified Bodies

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| **Position paper for the interpretation of device related changes in relation to a Notified Body Opinion as required under Article 117 of Medical Device Regulation (EU)2017/745** | |

# Introduction:

It is Team-NB's position that device component changes should be assessed in accordance with the principles applied to medical device substantial change assessments to confirm that the device component remains in compliance with Annex I of MDR 2017/745. This position paper is intended as a guide for the determination of proposed substantial changes to the device component of a drug device combination product.

# PART I: Background

## 1. Legislative background

Increasingly, medicinal products are being developed that incorporate either in an integral or non-integral manner, a medical device for the use and/or delivery of the medicine. In April 2017, the new Medical Devices Regulation (Regulation (EU) 2017/745 on medical devices (MDR)) was adopted by the European Union, updating the legal framework for medical devices. In addition to updated requirements for medical devices, Article 117 of the MDR has introduced amendments to Annex I, Directive 2001/83/EC concerning the documents that need to be submitted to Competent Authorities in the context of a marketing authorisation application.

According to Article 117 of MDR, an opinion issued by a notified body "on the conformity of the device component with the relevant general safety and performance requirements", i.e. a so-called NB Opinion (NBOp), is required in order to obtain marketing authorization for a medicinal product that forms a single integral product with a medical device. The Marketing Authorization Holder is, if a NBOp is applicable, responsible for submitting the NBOp in conjunction with the Marketing Authorization Application (or variation application) to the Drug Competent Authority. The NBOp of such a medicinal product includes an assessment of the device component with the relevant general safety and performance requirements (GSPR) set out in Annex I of MDR.

EMA <<Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) >>, published 21 October 2019 Rev.1 states there are cases where a (new or updated) NBOp is required if there are changes to the device submitted through a variation/extension application.

For integral drug-device combinations falling within the scope of Article 117, the MAH should determine whether updates to relevant documentation associated with the device in question are required. This may require a new or revised NBOp on the particular device against relevant GSPR's. It is important to note, changes to GSPR documentation and associated evidence do not automatically lead to a substantial change of the device component.

When considering changes to the device component, the MAH should also be cognisant of ISO 20069: 2019 Guidance for assessment and evaluation of changes to drug delivery systems along with ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management.
This Team-NB paper is intended to be used as part of a risk-based assessment of the proposed change, taking into account all relevant standards and guidance documents.

This position paper is not intended to supersede the variation regulation (EC 1234/2008) and MAH's must continue to apply the variation regulations as required, rather this position paper is to support MAH's in determining if a NBOp is required as part of a variation/extension application.

## 2. Scope and general considerations

This position paper is intended to provide the Notified Bodies' position on life cycle management of the device component of medicinal products falling within the scope of Article 117 of the MDR, i.e. integral drug device combination products. The purpose of this document is to create alignment between Notified Bodies and industry when considering whether a change to the **device component** is a substantial [1]change that could impact the GSPRs, and therefore would require review by a Notified Body under Article 117 of the MDR. This document constitutes an approach for identifying the regulatory consequences of implementing changes to the device component of drug-device combinations.

**The following changes are excluded from the scope of this guidance document:**

- **Changes with respect to the Quality Management System**
- **Changes to co-packaged devices**
- **Organizational or administrative changes e.g. manufacturing site, distributor, subcontractor, including their name, address and respective legal status**

Assessments should be made on a case-by-case basis taking e.g. into account the risk profile or the performance characteristics of the device component of the medicinal product.

This document represents the opinion of the members of the TEAM-NB Article 117 working group on the types of changes that may result in the need for a NBOp to be obtained to support a variation application

The marketing authorization holder (MAH) is responsible for analyzing whether any planned change to the device component will impact the GSPR or not.
The MAH may use this document, in addition to the change assessment guidance as outlined in life cycle management section of EMA/CHMP/QWP/BWP/259165/2019 to assess whether the foreseen change to the device component is considered a substantial change. If the analysis concludes that there is a substantial change to the device component requiring NBOp assessment, the request for a new or revised NBOp to assess

[1] The terms substantial and significant are understood to be interchangeable. For the purpose of this document the term substantial will be used.

the change against the relevant GSPRs should be submitted to a Notified Body designated under MDR for the type of the device under review.

In the scenario where an initial NBOp assessment does not exist for the device component, the compliance documentation to be submitted to the NB will need to cover all relevant GSPR of the device.

*Note:*

This document does not replace or affect regulatory documents, legislation, official guidelines or official regulations of the competent authorities and the European Commission. The definitions in this document are provided to clarify the meaning of terms used in this document only. They do not replace or in any way affect definitions from regulatory documents, legislation, guidelines or official regulations. This document may be overruled by future publications from the EMA or EU Commission.

This is a position paper to support in the risk-based classification of changes to the device component. The Notified Body cannot be held responsible where a different interpretation concerning a substantial change of the device component may occur following further guidance from EMA, European Commission or Drug Competent Authority. The Drug Competent Authority is and remains responsible for the approval of the drug-device combinations, including the approval of any relevant variations.

## 3. Product changes

A change of the device component of the medicinal product is understood to be substantial or significant if it may affect the device conformity with the General Safety and Performance Requirements.

Any change to the intended use which results in a change of device conformity with applicable GSPR will require a revised NBOp.

Apart from changes to the device, the MAH should also consider when changes to the medicinal product (e.g. changes to volume, viscosity, etc.) may impact the performance of the device; in such situations further verification and validation may be required.

Determining whether or not a change should be treated as substantial depends on multiple factors and a conclusion can only be drawn on a case-by-case basis. However, typical changes that may be considered substantial are (list not exhaustive):

- Device design specification changes (with the exclusions described in the next paragraph), e.g. widening specification limits or deletion of a specification parameter that has a substantial effect on the quality or safety of the device
- Device material changes, if the new material does not fulfill the same specifications or carries a significant risk (e.g. long term invasive)
- Changes in suppliers of device related materials/components (e.g. new supplier for a new material)
- Component changes, if the new component does not meet the same specifications as previously assessed one or carries a significant risk
- Changes to the operating principles (e.g. replacement of injection force's mode of action from spring-driven to gas-driven)
- Changes to shelf life for implantable or ingestible devices where the protocol has not been previously approved
- Software changes (with the exclusions described below)

- Changes in test procedure of a measuring or administration device
- Changes to built-in control mechanism
- Changes to the sterilization method, particularly for implantable or ingestible devices
- Changes to device materials of human /animal / biological origin
- Changes in colorants/ adhesives/lubricants/preserving agents or any other additives which are in contact with drug substance and/or patient
- Any change that introduces new hazards or negatively alters the benefit-risk profile
- Manufacturing changes which impact compliance with GSPR

Typical changes that may not need a NBOp are:

- Tightening of specifications within the already assessed range
- Material changes where the material is not in contact with the medicinal substance and/or patient, when the new material fulfills the same specifications as the previously assessed one
- Component changes, when the new component meets the same specifications as previously assessed, with the exception mentioned above
- Software changes when:
    - they are aimed at correcting errors in order to bring the system back within specifications (e.g. bug fixes)
    - they only modify the user interface with negligible risk of impacting diagnosis, therapy or functionality
    - they only introduce non-therapeutic and/or non-diagnostic features (e.g. printing, improved image clarity, etc.)
- Changes to the shelf life, when validated using a notified body assessed protocol or method, excluding implantable or ingestible devices.

To facilitate a harmonized judgement of the substantial of changes, the following flowcharts (see Part II) have been developed.

# PART II: Flow-charts and how to use this document

The document contains a detailed description of changes to the intended purpose and changes to the device component of a medicinal product which are considered substantial in the context of a NBOp according to Article 117 of the MDR.

The MAH may use this document to assess whether the change that they intend to make to the device component is a substantial change in the design, intended purpose, sterilization method, packaging or software. The MAH is strongly advised to actively engage up front with the drug competent authority in the final decision whether involvement of a Notified Body is necessary as part of the variation procedure. If the analysis concludes that there is a substantial change in the design or intended purpose requiring NBOp assessment, the request for a NBOp to assess the change against the GSPRs should be submitted to a Notified Body designated under MDR 2017/745 for the type of the device under review.

In addition to the example changes in described Part III, the MAH can refer to the flowcharts, which show various types of changes. These flowcharts support the MAH to evaluate whether the changes made to the device component are considered substantial or not.

The following flowcharts are described:

- Main Chart: Change of an existing device component in a drug-device combination product
- Flowchart n°1: Substantial Changes in the intended purpose
- Flowchart n°2: Substantial Changes in the design
- Flowchart n°3: Substantial Changes of a component or a material
- Flowchart n°4: Substantial Changes of sterilization method or packaging with impact to the sterilization
- Flowchart n°5: Substantial Changes in the design - Software Changes

In case of changes to the intended purpose of the device part, Flowchart n°1 is applicable.

When the plan to change concerns the design of the device, the MAH should use Flowchart n°2.

After having used Flowchart n°2 and when the proposed change project of the design of the device part concerns more particularly a component or a material, the method of sterilization or the packaging necessary to preserve sterilization or software, the MAH should refer the corresponding Flowchart that has been developed in addition to Flowchart n°2.

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

The outcome of the flow chart is either to recommend that a new/ revised NBOp is provided or not. This has been developed based on the expertise of Team-NB. The final decision is the MAH's who has more context of the change including relative risk and GSPRs affected.

## Definitions

*Substantial change*: A change is considered substantial change when it is likely to have an impact in terms of:

- Device safety and/or performance;
- Compliance with the relevant GSPR(s) of the applicable Regulation;
- Device related claims and intended use.

*Intended purpose* means the use for which a device component is intended according to the data supplied by the MAH on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the MAH in the clinical evaluation.

*Software* means the set of instructions used to control the actions or output of a medical device, to provide input to or output from a medical device, or to provide the actions of a medical device. This definition includes software that is imbedded or permanently a part of a medical device, software that is an accessory to a medical device

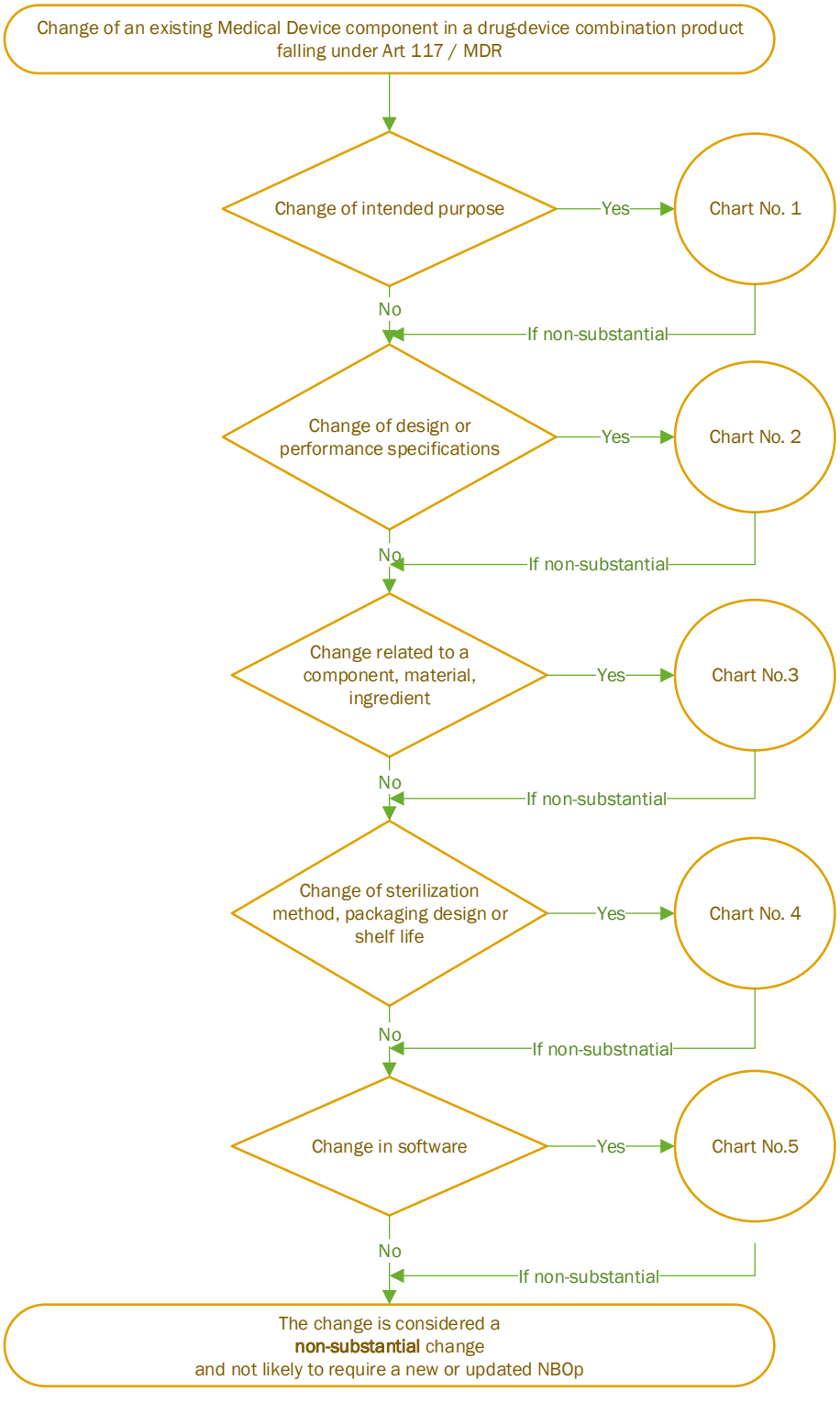
*Control mechanism* is a means of verifying or checking that the specifications or outputs of the device meet a standard or predetermined result. They are mechanisms put in place to maintain on-going control or regulate the output of a device.

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

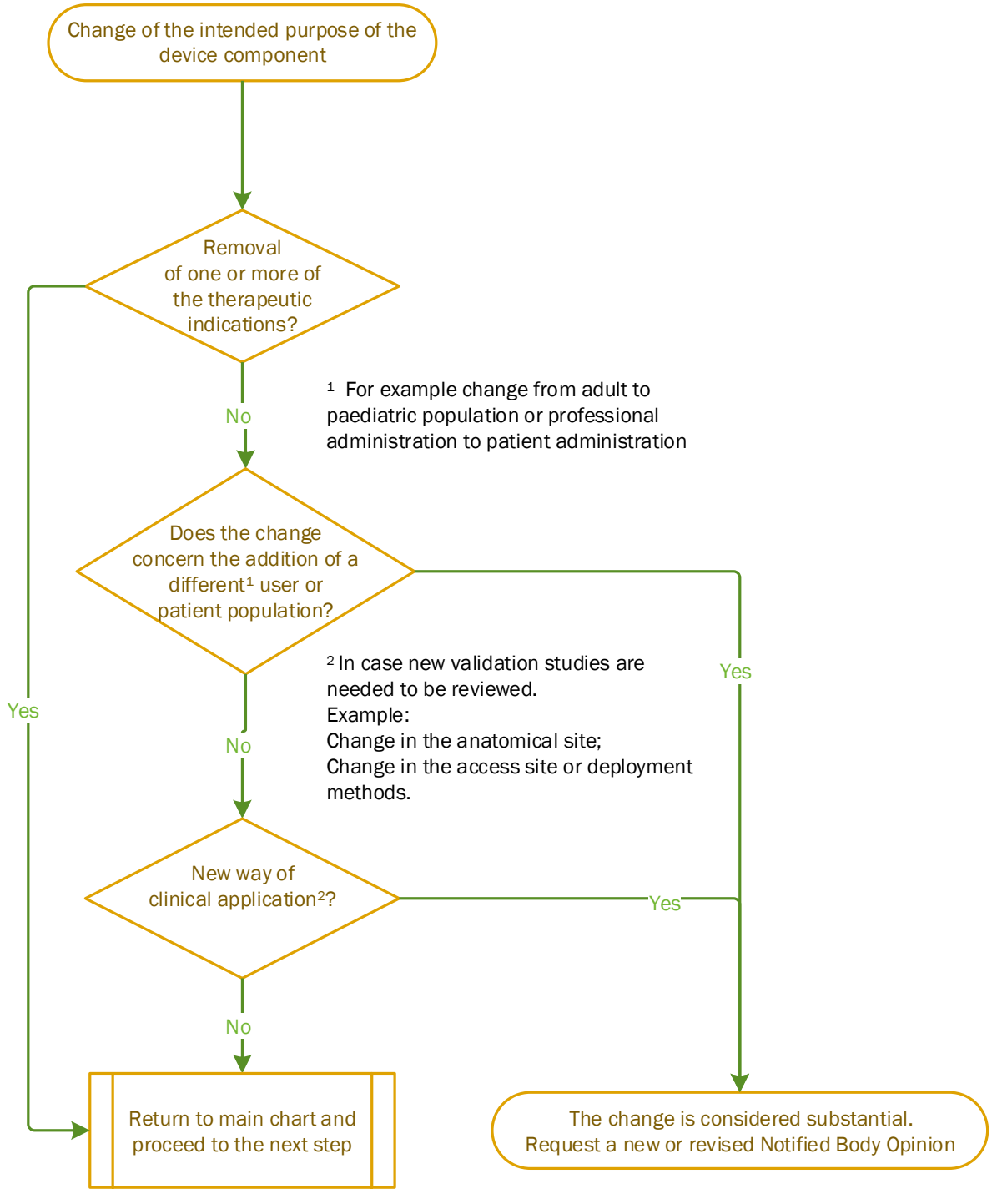
*Supplier* designates the company supplying the raw material or components to a finished device MAH.

*Variation applications* are used to obtain approval for a change to the terms of a drug marketing authorization.

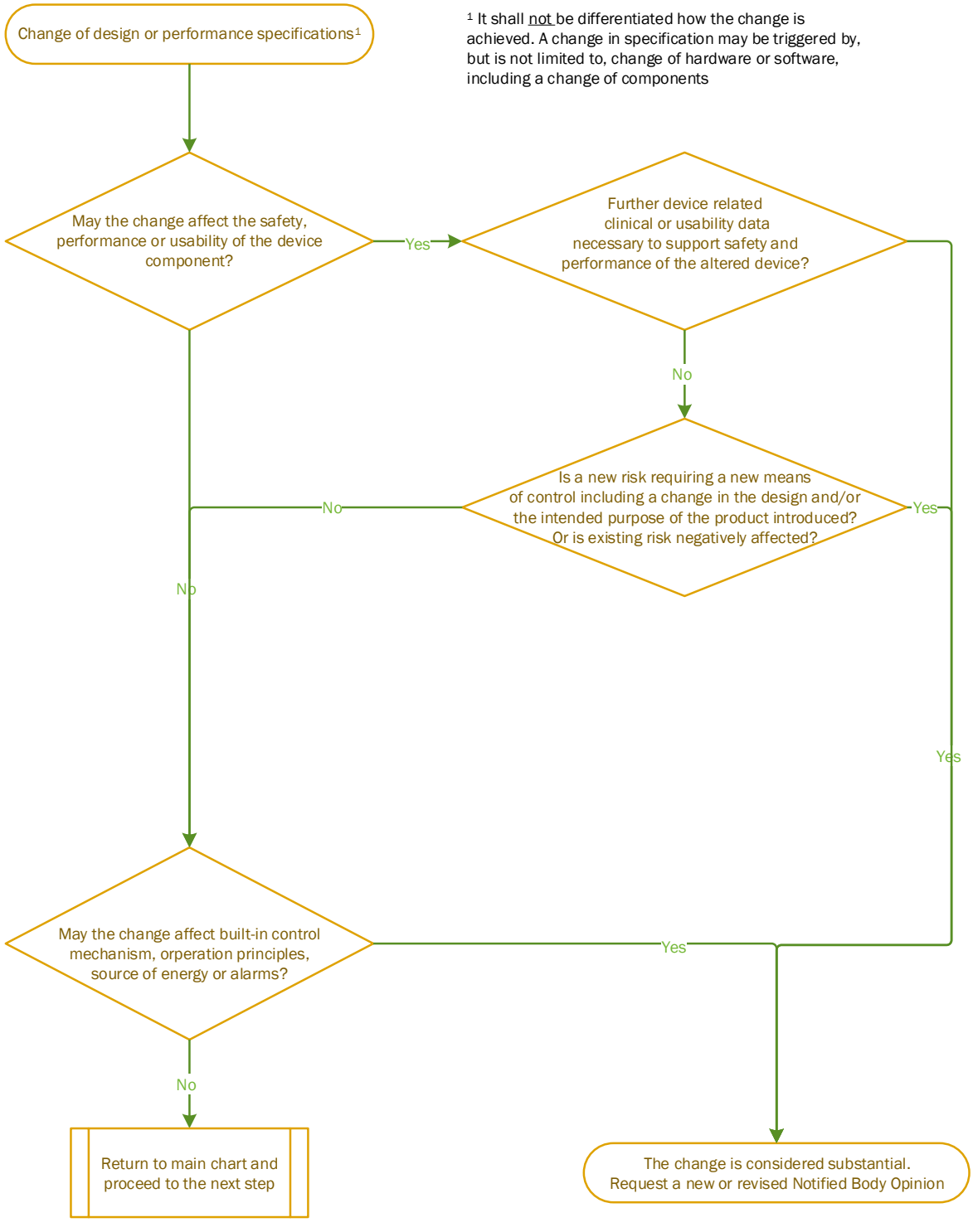
## Main Chart


Change of an existing Medical Device component in a drug-device combination product falling under Art 117 / MDR
Change of intended purpose
Yes
Chart No. 1
No
If non-substantial
Change of design or performance specifications
Yes
Chart No. 2
No
If non-substantial
Change related to a component, material, ingredient
Yes
Chart No.3
No
If non-substantial
Change of sterilization method, packaging design or shelf life
Yes
Chart No. 4
No
If non-substnatial
Change in software
Yes
Chart No.5
No
If non-substantial
The change is considered a non-substantial change and not likely to require a new or updated NBOp

## Flowchart n°1: Substantial changes in intended purpose



## Flowchart n°2: Substantial changes in the design or performance specification



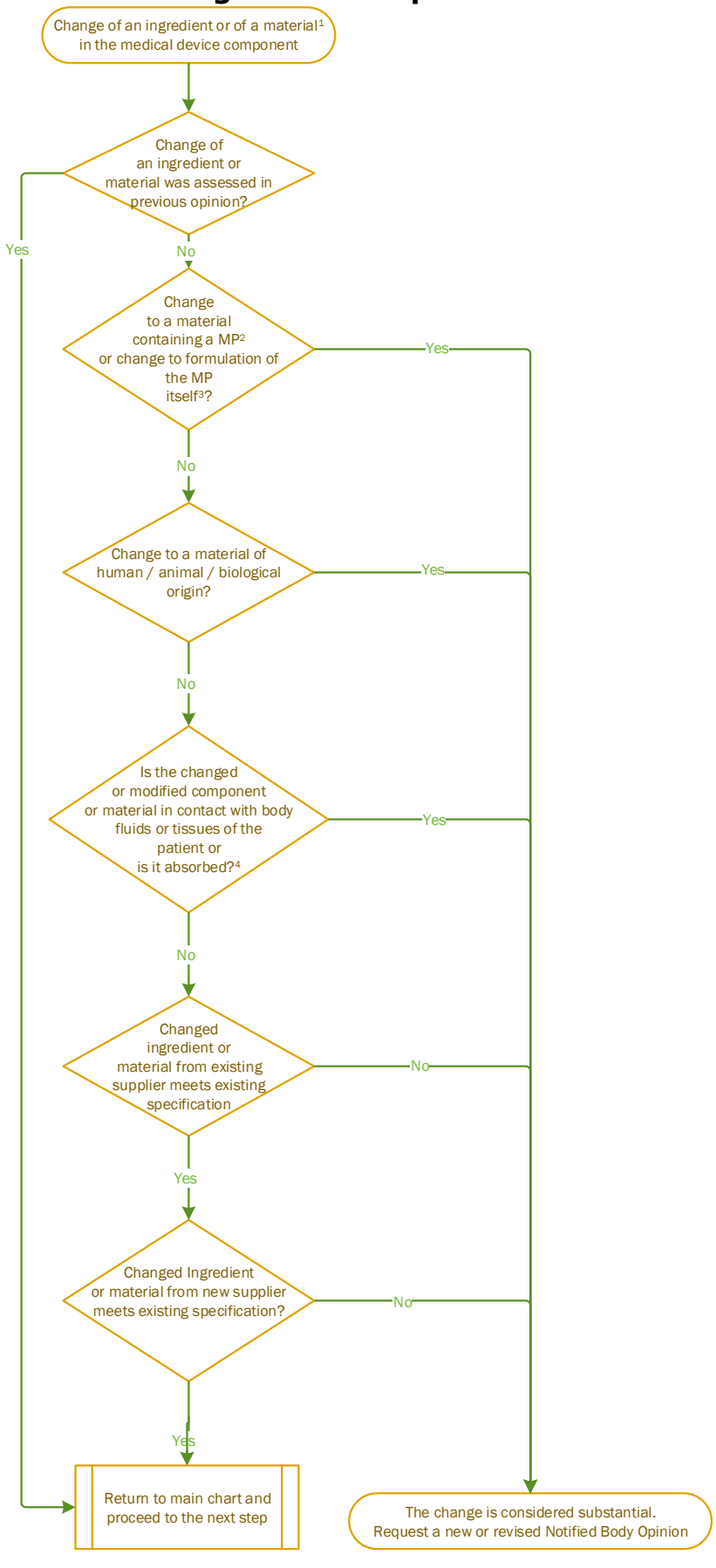
# Flowchart n°3: Substantial changes of a component or a material

[1] These relate to changes involving existing ingredients and materials. New ingredients or materials are considered substantial changes.

[2] MP:Medicinal product

[3] Including a change in its manufacturing process, beyond existing specification. A change in the characteristics oft he drug could impact the performance oft he device part (e.g. change in volume, change in viscosity)

[4] Example:
- Implantable device
- oral ingestible
- external communicating device



# Flowchart n°4: Changes of sterilization method/parameters, packaging design or shelf life

[1] It is expected that the drug competent authority will review the final sterilization of the drug-device combination. The NB will assess sterilised incoming components of the device part.

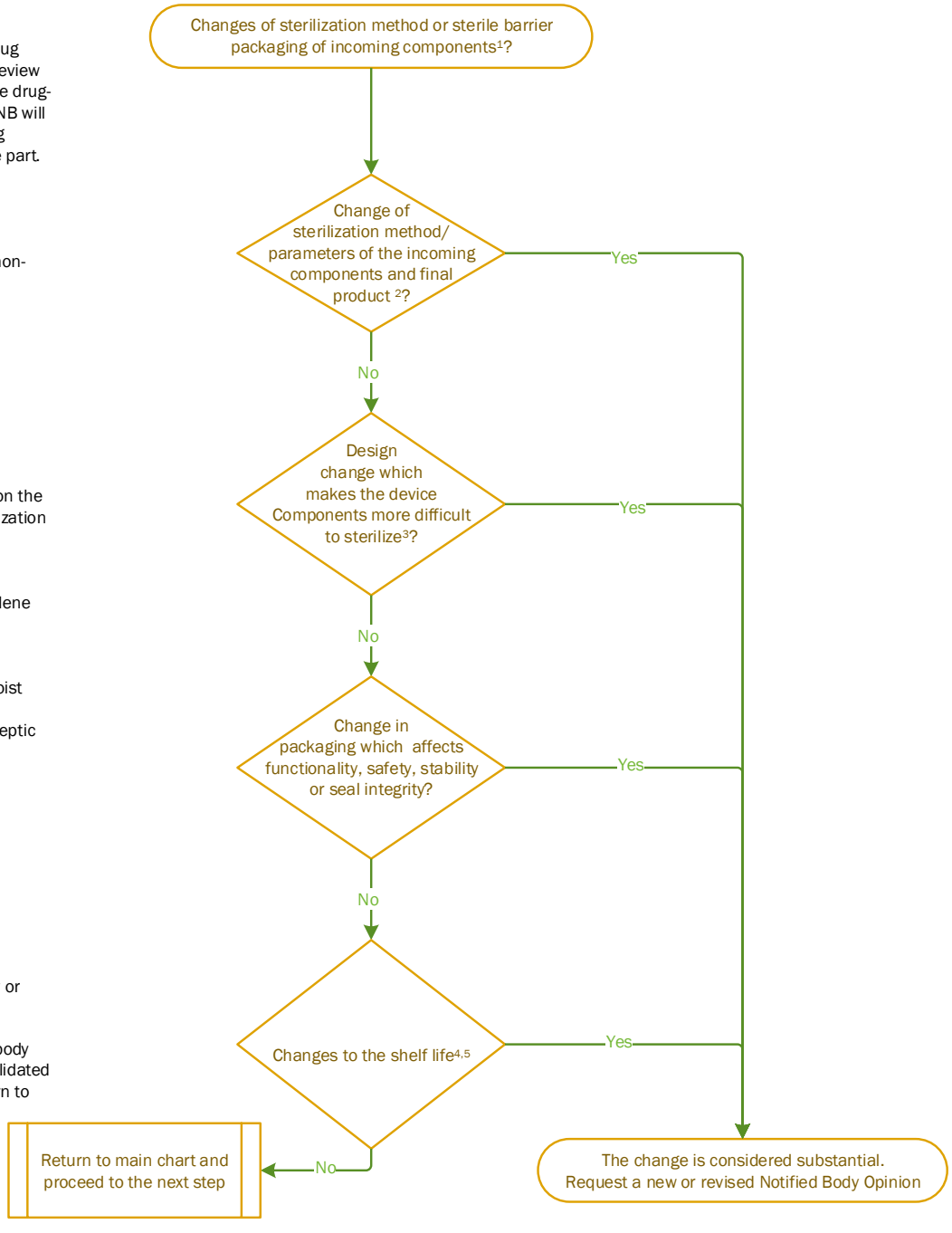
[2] Includes changes from non-sterile to sterile

[3] Guidance on assessing changes for their impact on the effectiveness of the sterilization process is provided in the respective sterilization standards such as:

- EN ISO 11135 (Ethylene Oxide),
- EN ISO 11137-1 (Radiation),
- EN ISO 17665-1 (Moist Heat),
- EN ISO 13408-1 (Aseptic Process).

[4] Shelf Life changes of implantable or ingestible devices will require a new or revised NBOp

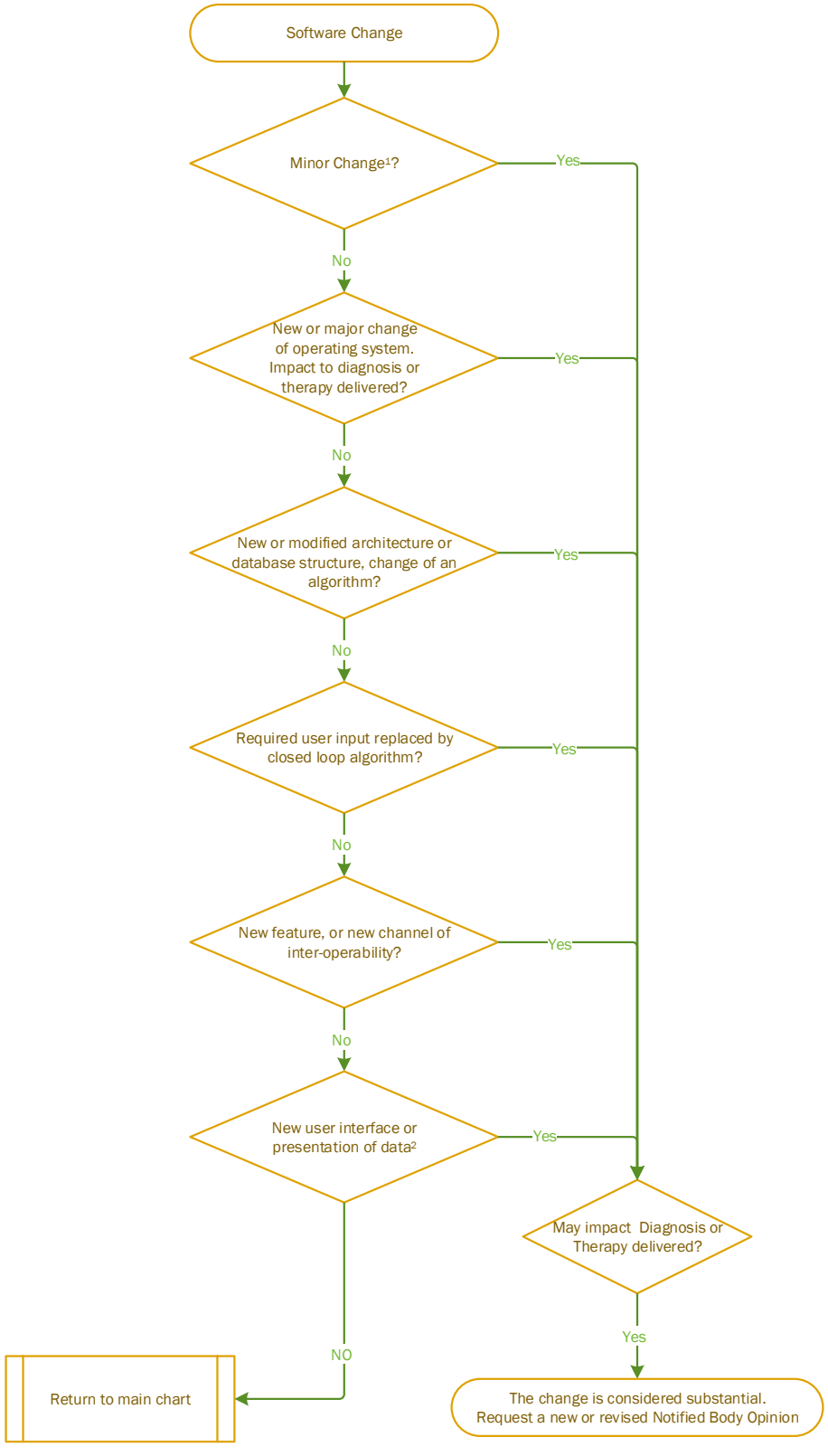
[5] unless using a notified body assessed protocol and validated method. In this case return to main chart



# Flowchart n°5: Substantial changes in the design – Software changes

[1] Minor changes without impact to diagnosis or treatment delivered may include:

- correction of an error which does not pose a safety risk (bug fixes),
- Security update (e.g. cyber-security enhancements, longevity calculations),
- appearance of the user interface,
- operating efficiencies.




[2] Presentation of data" goes beyond the appearance of the user-interface which may include new languages, layouts or graphics and is considered a minor change.
„Presentation of data" is connected to medical data which are presented in a new format or by a new dimension or measuring unit.

# PART III: Explanatory Notes and Examples

## Explanation 1: Substantial changes in intended purpose

See Flowchart n°1

The following examples are considered substantial changes in the intended purpose:

- Changes regarding a new indication or clinical practice resulting in addition of new final users or new patient target group. A change which results in the need to generate new usability data or reassessment of existing usability data and risks will likely be considered substantial. For example, change from health care professional to patient administration or change from adults to children, also a change from an intramuscular injection route to an intra-venous injection route

## Explanation 2: Changes in the design

See Flowchart n°2

Generally, any change in medical device design is considered to be a substantial change when it has an impact in terms of safety, performance or usability and this impact requires the implementation of at least one of the following actions:

- Analysis of further clinical data (e.g. device related performance data, clinical investigation, post market clinical data), relating to the device component;
- Analysis of further usability data, e.g. human factors studies;
- Analysis of new risks introduced due to the change performed with need to have additional control means;
- Analysis of an already identified risk that is negatively impacted by the change.

Taking this into account, the Notified Body may consider the following changes as substantial:

- Change of built-in control mechanism;
- Change in operating principle or mode of action;
- Change in type of energy source of medical device (e.g. transition from a spring activated injection mechanism to an electrical activation injection mechanism).

## Explanation 3: Changes related to a component or a material of the device

See Flowchart n°3

Any change impacting a component or material of the device is considered substantial when it meets at least one of the following conditions:

- the component or material is human/animal/biological origin;
- the change impacts the quality, safety or efficacy of a pharmaceutical substance;
- the component or material is in contact with body fluids or tissues *;
- the component or material is absorbed*.

* For this type of component or material, the change is not substantial if one of the following criteria is met:

- Modified or replaced component or material comes from the same supplier and meets the same specifications as the original component or material;
- The component or material comes from a new supplier and meets the same specifications as the component or material provided by the original supplier.

The demonstration of equivalence shall relate to characteristics and performances of the component or material. Differences shall not affect the characteristics or specifications of the finished device component.

## Explanation 4: Changes of sterilization method or sterile barrier packaging

See Flowchart n°4

The following changes are considered substantial changes in the design:

- Change of sterilization mode (e.g. the device is sterilized by irradiation and MAH wants to sterilize its device with ethylene oxide)
- Change of a material of the device having an impact on sterilization* (e.g. addition of a new material known to retain a larger quantity of residues of ethylene oxide);
- Change in the design of the device having an impact on the sterilization* (e.g. change of lumen dimension for an aspiration catheter or a drip chamber for an Infusion set);
- Change in packaging may adversely affect the function, safety, stability of the device or the integrity of the seal;
- Change of the lifetime and/or shelf-life validated by other methods or protocols than those which have been assessed, excluding implantable or ingestible devices.

*For Ethylene Oxide sterilization, please refer to standard EN ISO 11135 and guidance document AAMI TIR 28. For Radiation sterilization, please refer to standard EN ISO 11137-1. For Moist heat sterilization, please refer to EN ISO 17665-1. For Aseptic Process sterilization, please refer to EN ISO 13408-1 & 7.

## Explanation 5: Software changes

See Flowchart n°5

Changes to software are considered substantial when the functionality related to the diagnosis or therapy delivered to the patient are modified (e.g. change of usage or interpretation parameters) and relate to at least one of the following elements:

- major change of operating system requires a change in functionality of the software or system;
- new operating system (e.g. the software is only compatible with Android and MAH wants to extend the compatibility to iOS);
- new or modified architecture or database structure;
- change which impacts the control of the device; that may alter diagnosis or therapy delivered to the patient;
- change of algorithm or data presentation impacting the diagnosis or therapy delivered;
- introduction of a new diagnostic or therapeutic feature;
- introduction or removal of an alarm; such that a response to the new configuration may change the treatment of the patient in comparison to the previous version of the software;

- data user input is no longer necessary because the changed software makes a closed-loop decision;
- 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
- new channel of inter-operability.

Software changes that have no impact on the diagnosis or therapy delivered to the patient can be considered as changes related to the following, and as such are considered non-substantial:

- bug fixes
- an error correction that does not present risk for device safety and does not modify software or the system functionality;
- a safety update (e.g. an improvement related to cyber security)
- a new non-medical functionality, a new feature that does not modify the software structure or responsible for medical functionality;
- appearance of the user interface, (new languages and layouts or graphics not related to medical data);
- disabling feature that does not interact with other medical features

## Example 1:

An implantable integral device/medicinal product is approved with a 2-year shelf life. The MAH intends to extend it to 3 year. The validation is conducted following different protocol and test methods accepted by the Notified Body for approval with a 2-year shelf life.

- Substantial change to device component? Yes
- New or revised NBOp is required? Yes

## Example 2:

A drug eluting inter-uterine device is sterilized by ETO at the facility XYZ. The MAH intends to introduce facility ABC as a second provider of ETO sterilization. The validation of the sterilization process at ABC is conducted following same protocol and test methods accepted by the Notified Body for the approval of sterilization at XYZ.

- Substantial change to device component? No
- New or revised NBOp is required? No

## Example 3:

A stopper used in a pre-filled syringe is ETO sterilized and the MAH intends to change the process to introduce a gamma sterilization process, although maintaining a SAL of $10^{-6}$

- Substantial change to device component? Yes
- New or revised NBOp is required? Yes

## Example 4:

The raw material supplier for an implantable integral device/ medicinal product is discontinuing production so the MAH intends to replace the existing material with a new one whose characteristics fall within the same range, provided by a different supplier

- Substantial change to device component? Yes
- New or revised NBOp is required? Yes (being permanently implanted, the material carries a significant risk)

## Example 5:

The raw material for a breath actuated inhaler is moved from a site in Mexico to a new facility in Costa Rica. The raw material is manufactured through the same process and fulfil the same specifications.

- Substantial change to device component? No
- New or revised NBOp is required? No

## Example 6:

The shell of an autoinjector is made of medical grade acrylic polymer. The raw material supplier is discontinuing production, so the MAH intends to replace the material with a new acrylic polymer, whose characteristics fall within the same specifications, provided by a different supplier

- Substantial change to device component? No
- New or revised NBOp is required? No

## References


- Medical Device Regulation (MDR) 2017/745

- Directive 2001/83/EC Medicinal Product for Human use

- EMA <<Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746)>>

- ISO 20069: 2019 Guidance for assessment and evaluation of changes to drug delivery systems

- ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management

- (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

- 2013/C223/01 Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008

- EN ISO 11135 (Ethylene Oxide),
- EN ISO 11137-1 (Radiation),
- EN ISO 17665-1 (Moist Heat),
- EN ISO 13408-1 (Aseptic Process).
- EN ISO 13408-7 (Aseptic Process - Alternative processes for medical devices and combination products)