MDCG 2022-6

Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR

May 2022

This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission.

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1 Introduction

Article 110(3) of Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR), as amended by Regulation (EU) 2022/112[1], states that under certain conditions the following devices may be placed on the market or put into service after the date of application of the IVDR, i.e. 26 May 2022, until the end of the different transition periods specified in Article 110(3) IVDR:

- devices which have a valid certificate issued by a notified body under the Directive 98/79/EC on *in vitro* diagnostic medical devices (IVDD), and
- devices for which a declaration of conformity was drawn up prior to 26 May 2022 in accordance with the IVDD and for which the conformity assessment procedure pursuant to the IVDR (contrary to the IVDD) requires the involvement of a notified body.

In line with Q&A 9 of the CAMD's FAQ – IVDR Transitional provisions[2], the certificates covered by Article 110(3) of the IVDR include all certificates which are commonly issued by notified bodies[3] with reference to the IVDD.

The conditions for the application of the transitional provisions in Article 110(3) IVDR are that the devices continue to comply with the IVDD[4] and that there are no significant changes in the design or intended purpose of the device after the date of application of the IVDR. Therefore, it is important for manufacturers and notified bodies to have a clear understanding as to what changes to design or intended purpose would be considered 'significant' under Article 110(3) IVDR.

To the extent that devices subject to the transitional provisions in Article 110(3) IVDR are covered by certificates issued by a notified body in accordance with the IVDD, it is essential for IVDs to be placed on the market that those certificates remain valid[5] following changes that are not significant with regard to design or intended purpose and that the required appropriate surveillance is carried out by the notified body that issued the certificate. Manufacturer and respective notified body should agree on the latter on a contractual basis.

This guidance document is based on MDCG 2020-3 Guidance on significant changes regarding the transitional provision under Article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD. Where appropriate, this guidance

1 OJ L 19, 28.1.2022 p.3.
2 CAMD Transition Sub Group, FAQ – IVDR Transitional provisions, V1.0, 17.1.2018.
3 According to Article 110(1) IVDR, from 26 May 2022 any publication of a notification in respect of a notified body in accordance with Directive 98/79/EC becomes void. Irrespective of this, the term 'notified body' is used throughout this document also for notified bodies previously designated under Directive 98/79/EC.
4 However, the requirements of IVDR relating to post-market surveillance, market surveillance, vigilance, registration of economic operators and of devices shall apply to the devices and replace the corresponding requirements in the Directive.
5 This does not exclude the possibility that during the transition period an EC certificate for the manufacturer's approved quality system issued in accordance with Annex IV or Annex VII IVDD, which has become invalid, is replaced by a EU QMS certificate issued in accordance with Annex IX, chapter 1, IVDR, provided that the EC design examination certificate issued under Annex IV, section 4, IVDD or EC type-examination certificate issued under Annex V IVDD remains valid.

document is adapted to the IVD sector and it takes into account experience gained with the application of MDCG 2020-3[6].

2 Scope

This guidance document is intended to provide clarification on the concept of 'significant changes in the design and intended purpose' under IVDR Article 110(3). It concerns manufacturers of devices that are compliant with Directive 98/79/EC and that are placed on the market or put into service after 26 May 2022 during the transition period in accordance with Article 110(3) IVDR, irrespective of whether or not those devices required notified body involvement under the IVDD.

This guidance document does not elaborate on the process for manufacturers' submission and notified bodies' assessment of changes to the approved design[7] or substantial changes to the approved quality system or the product-range covered[8] that are part of the conformity assessment process and surveillance defined by the relevant notified body under the IVDD.

3 Changes to Directive certificates

It is important to highlight that no issuing of new IVDD certificates is allowed under IVDR Article 110(3)[9] (see also section 4.1). In particular, if the manufacturer wishes to make a 'significant change in design or intended purpose' within the meaning of IVDR Article 110(3), the implementation of such a change would prevent the manufacturer from placing the device on the market under the IVDD in accordance with that provision.[10]

[6] At its meeting on 21 March 2022, the MDCG approved the annual work programme of its NBO sub-group according to which MDCG 2020-3 should be aligned with the present guidance where needed.

[7] See Annex III, sect. 6.3. IVDD: "*The applicant shall inform the notified body …. of any significant change made to the approved design*"; Annex IV, sect. 4.4. and Annex V, sect. 6.1. IVDD: "*Changes to the approved design must receive further approval from the notified body …*"; Annex IV, sect. 4.5. and Annex V sect. 6 IVDD: "*The manufacturer shall inform the notified body without delay if it has obtained information about changes to the pathogen and markers of infections to be tested …*".

[8] See Annex IV, sect. 3.4. IVDD: "*The manufacturer must inform the notified body ... of any plan for substantial changes to the quality system or the product-range covered";* Annex VII, sect. 3.4. IVDD: "*The manufacturer shall inform the notified body ... of any plan for substantial changes to the quality system*".

[9] This does not mean that notified bodies are not allowed to e.g. suspend, re-instate, restrict or withdraw such certificates. Such activities should be communicated as written decisions / statements. Moreover, notified bodies should document corrections or additions to existing certificates resulting from changes that are not significant changes to design or intended purpose (e.g. administrative changes) (see section 4.1).

[10] Should the manufacturer wish to place such a changed device on the market, they may do so under the IVDR.

4 Assessment whether changes are 'significant changes in the design or intended purpose' in accordance with IVDR Article 110(3)

4.1 General

In order to benefit from the transition periods provided in Article 110(3) IVDR, devices may not undergo any significant change in the design or intended purpose after the date of application of the IVDR, i.e. 26 May 2022.

This condition consists of two elements:

- there is a change in the design or intended purpose and
- that change is non-significant.

That means that changes that do not concern the design or intended purpose are out of scope of Article 110(3) IVDR. Equally, changes that concern the design or intended purpose only fall under Article 110(3) IVDR if they are considered 'significant'.

The manufacturer always remains responsible for providing evidence that changes neither affect the design nor the intended purpose. When a change is likely to affect the design or the intended purpose of the device, the significance of such a change should be assessed case-by-case providing evidence for the outcome of the assessment. The manufacturer must be able to justify their decision when the changes are considered to be non-significant. The justification shall be documented and made available to a competent authority when requested.

If a change is not a significant change in design or intended purpose under IVDR Article 110(3), the implementation of such a change is allowed during the transitional period without the need for certification under the IVDR. In such cases, the manufacturer needs to comply with the documentation requirements of the IVDD, i.e. the updated technical documentation must allow assessment of the conformity of the product with the applicable requirements.

Additional considerations for devices covered by a certificate issued by a notified body

In line with the agreed arrangements for notification of changes between the manufacturer and the notified body according to the IVDD (e.g. contractual relationships, approved procedures)[11], changes and their implementation will be verified by the notified body as part of the surveillance activities, or following a manufacturer's submission for prior approval. The outcome of this verification will determine whether a certificate in accordance with the IVDD remains valid according to Article 110 IVDR. In case of doubt as to whether a given change is significant, manufacturers should ask their notified body.

The certificate should not be amended. However, the notified body that issued the certificate in accordance with the IVDD may confirm in writing, after having reviewed the manufacturer's description of the (proposed) change, that the implementation of the change does not

[11] Those change notification procedures may need to be adjusted in accordance with the principles outlined in this guidance. This should be subject to notified body assessment within the surveillance activities according to IVDR Article 110(3).

represent a significant change in design or intended purpose under IVDR Article 110(3) and that the related IVDD certificate remains valid after the date of application of the IVDR, but no longer than its expiry date or 26 May 2025, whichever comes first. Such written confirmation corrects or complements information on an existing certificate but does not represent the issuance of a 'supplemented certificate', since this is prohibited as mentioned in Section 3. In case of requests from authorities, the manufacturer should number such letters received from the notified body and submit them together with the certificate.

Where the conformity assessment procedure under the IVDD requires the quality management system (QMS) to be approved by a notified body, the manufacturer must observe that the conditions for which the certificate was granted are maintained. In any case, changes to the QMS continue to be subject to the agreed notification procedure between manufacturer and notified body.

4.2 Changes not concerning the design or intended purpose

Changes concerning the manufacturer's organisation (administrative changes) or changes concerning the manufacturing process should generally not be considered changes in the design or intended purpose within the meaning of Article 110(3) IVDR, even if they need to be reflected in the information to be supplied with the device (e.g. label or instructions for use).

This includes for example:

- changes of the manufacturer's name, address or legal form, including a merger or acquisition involving the manufacturer;
- changes in relation to the authorised representative;
- relocation or addition of new manufacturing sites, including when it affects subcontractors or suppliers;
- changing the supplier of a material, ingredient or component, provided the specifications of the new material, ingredient or component do not change;
- adding or replacing a new material number for logistic reasons without changing the material;
- changes to outer packaging (e.g. size, material, layout) that do not adversely affect the stability, sterility or microbiological state of the device;
- new process validation as part of manufacturing improvements or scale-up of manufacturing.

Changes of the QMS, such as changes in the monitoring and control of production and operations environment, generally do not impact the design or intended purpose either, provided that the conditions for which the conformity assessment certification was granted are maintained.

4.3 Changes in the design or intended purpose

4.3.1 Design and intended purpose

As the devices that are placed on the market in accordance with the transitional provision laid down in Article 110(3) IVDR need to be in compliance with Directive 98/79/EC, the benchmark for determining their design and intended purpose, as well as any possible change, should be the IVDD.

While the IVDD does not define the '**design'** of a device, the '**intended purpose'** means "*the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions for use and/or in promotional materials*" (Article 1(2), point (h), of the IVDD).

4.3.2 Significance of changes

Not all changes concerning the design or intended purpose would automatically have to be regarded as 'significant'. Whether or not a change is significant has to be assessed case by case.

To facilitate a harmonised judgement of the significance of changes, this guidance document provides several flowcharts in the **Annex**. The assessment of a proposed change using the main flowchart and any of the applicable sub-charts is intended to assist manufacturers, notified bodies and market surveillance authorities in deciding whether or not a change of the design or intended purpose of the device is to be considered significant under IVDR Article 110(3).

A change is considered a non-significant change of design or intended purpose per IVDR Article 110(3) if the answer to every question in a sub-chart leads to 'non-significant change' also when returning to the main chart. On the contrary, if any sub-chart delivers the result 'significant change', the change being assessed is a 'significant change in design or intended purpose' according to the IVDR Article 110(3).

4.3.2.1. General considerations

As a general rule, the following changes in design and/or intended purpose should not be regarded as 'significant':

- changes related to corrective actions assessed and accepted by the competent authority (see also Q&A 15 of the CAMD's FAQ – IVDR Transitional provisions regarding design changes; the same approach should apply also to changes related to the intended purpose)[12];

[12] 'Corrective action' refers to corrective action as defined in Article 2(70) IVDR, i.e. any "*action taken to eliminate the cause of a potential or actual non-conformity or undesirable situation".* This includes 'field safety corrective actions' (FSCA) as defined in Article 2(71) IVDR. 'Competent authority' should generally be the authority of the Member State in which the manufacturer or its authorised representative is established. It can either be a competent authority for vigilance in accordance with Article 82 IVDR or a competent authority for market surveillance in accordance with Article 88 IVDR. The role of the competent authority is to assess and determine the acceptability of the (field safety) corrective action proposed by the manufacturer aimed at preventing or reducing safety risks regardless of whether the (field safety) corrective action describes a change of design or intended purpose. The assessment and acceptance of a (field safety) corrective action by a

- correction of spelling mistakes or merely editorial changes of the information to be supplied with the device (e.g. label or instructions for use);
- updates of the information to be supplied with the device (e.g. label or instructions for use) if they are required by law other than the IVDR (e.g. CLP Regulation (EC) 1272/2008 read in conjunction with Annex I, section 8.3. IVDD) are mere clarifications and do not adversely affect the devices' safety and performance in relation to existing or new risks.

4.3.2.2 Changes in the intended purpose – Chart A

Regarding **changes of the intended purpose** the following principles should apply (see chart A):

Non-significant change:

- limitation of the intended purpose (see Q&A 15 of CAMD's FAQ – IVDR Transitional provisions), such as restricting the target population, specimen type, specimen location.

Significant change:

- extension of the intended purpose, such as:
  - additions regarding what is detected and/or measured, such as addition of a new genotype to a human papillomavirus assay, necessitating new primers[13];
  - additional functions of the device, such as screening, monitoring, diagnosis;
  - for companion diagnostics: extension of the target population(s) or of the tissue type or associated medicinal products;
  - addition of specimen type(s).
- any other major change of the intended purpose, such as:
  - change of assay type, e.g. from screening assay to confirmatory assay or from qualitative to quantitative assay;
  - change of the intended user, e.g. from professional user to lay user;
  - change of operation from automatic to manual or *vice versa*;
  - change of specimen type(s).

When assessing whether the intended purpose is being changed, changes in the label or instructions for use that are linked to the use for which a device is intended (e.g. limitations, warnings) should be considered.

competent authority does not exempt the manufacturer from submitting changes to the relevant notified body under the IVDD nor the notified body from assessing the change in line with the agreed arrangements (see also sections 2 and 4.1 of this guidance). The manufacturer is responsible for implementing the (field safety) corrective action, including changes in the design or intended purpose, if needed.

[13] The confirmation that a device intended to detect a given pathogen remains suitable to detect also a new strain of that pathogen should not in itself be regarded as a significant change of design or intended purpose (e.g. a confirmation that a device intended to detect SARS-CoV-2 remains suitable for detection of a new variant).

4.3.2.3 Changes in the design – Charts B to E

Changes concerning software, ingredients or materials, or sterilisation also concern the design of the device. Specific flowcharts (C, D, E) are intended to assist in assessing whether changes in those areas should be considered significant changes in the design.

Regarding **changes of the design** the following principles should apply (see chart B):

Non-significant change:

- changes of the design that do not alter the device's operating principle[14], that do not adversely affect the safety or performance and that do not negatively affect the risk/benefit ratio of the device:
    - changes in incubation times and temperatures;
    - changes in the processing steps of the method (e.g. a new washing step);
    - use of a new PCR cycler which is more efficient in controlling the temperature;
    - adding PCR cyclers from other producers as being compatible with a particular PCR assay;
    - change of the swab intended to be used with a device;
    - replacement of the ELISA instrument;
    - extension or reduction of shelf life of a non-sterile device[15];
    - change from refrigerated to room temperature storage conditions;
    - change in internationally agreed reference values;
    - change of instructions for use to refer to better precision of the device based on data obtained as a result of post-market surveillance or addition of new interfering or cross-reacting substances;
    - clarifications of labelling or instructions for use;
    - change of number of tests in the kit configuration.

  Note: These examples are valid only provided that the change does not adversely affect the safety or performance and that it does not negatively affect the risk/benefit ratio of the device.

Significant change:

- changes that alter the device's operating principle[16]:

  Examples:
    - change from immunofluorescence to ELISA;

[14] Operating principle – the overall assay or testing method(s), mechanism(s) or principle(s) of measurement, including the detection principle, which the device uses to achieve its intended purpose, (e.g. enzyme-linked immunosorbent assay (ELISA) with chemiluminescence-based detection, polymerase chain reaction (PCR), isothermal DNA amplification).
[15] For extension of shelf life of sterile devices, please see chart E.
[16] See footnote 14.

- change from immunochromatography with subjective visual detection to immunochromatography with detection by automated reader;
- change from high-performance liquid chromatography (HPLC) coupled with time-of-flight mass spectrometry to HPLC coupled with orbitrap mass spectrometry;
- change from photometric measurement into liquid chromatographic based or proton nuclear magnetic resonance spectroscopy (NMR) measurement;
- change from immunoturbidimetry measurement to colorimetric measurement.

- changes that adversely affect the safety or performance and negatively affect the risk/benefit ratio of the device, even if they do not alter the device's operating principle:

  Examples:

  - change of instructions for use to refer to reduced sensitivity of the device based on data obtained as a result of post-market surveillance;
  - alteration of assay-specific cut-off values resulting in decreased specificity.

Software changes[17] **– Chart C**

Regarding **software changes** the following principles should apply (see chart C):

Non-significant change:

- correction of an error which does not pose a safety or performance risk (bug fixes);
- updates or upgrades of standard third party operating systems, e.g. Microsoft windows; iOS;
- security update (e.g. cyber-security enhancements, longevity calculations);
- appearance of the user interface (e.g. new languages, layouts or graphics);
- operating efficiencies;
- changes to enhance the user interface without changes in performance.

Note: These examples are valid only provided that the change does not adversely affect the safety or performance and that it does not negatively affect the risk/benefit ratio of the device.

Significant change:

- new or major change of operating system or any component;
- new or major modification of architecture or database structure, change of algorithm;
- addition of a new database with new content that is used to compare genetic assay results with;
- required user input replaced by closed loop algorithm;

[17] This section should be considered irrespective of whether the software is stand-alone or used in combination with a device.

- presentation of medical data in a new format or by a new dimension or measuring unit.

Changes related to an ingredient or material – Chart D

Regarding **changes of ingredients or materials** the following principles should apply (see chart D):

Non-significant change:

- changes of an ingredient or material that is not essential for the device's operating principle, that do not adversely affect the safety or performance and that do not negatively affect the risk/benefit ratio of the device:
    - replacing a preservative;
    - use of a new buffer whose pH is slightly different and more adapted to the assay;
    - substitution of a chemical substance in order to comply with the REACH Regulation (EC) No 1907/2006.

Note: These examples are valid only provided that the change does not adversely affect the safety or performance and that it does not negatively affect the risk/benefit ratio of the device.

Significant change:

- changes of an ingredient or material that is essential for the operating principle of the device:
    - primers for PCR;
    - capture antibodies / antigens for immunoassay;
    - detection marker (e.g. fluorescent, chromogenic, chemiluminescent marker) for chromatography.
- changes of an ingredient or material that adversely affect the safety or performance and that negatively affect the risk/benefit ratio of the device:
    - substitution of a chemical substance in order to comply with the REACH regulation with an adverse impact on performance of the device.

Changes related to sterilisation – Chart E

Regarding **changes related to the sterilisation method or related to the design or the packaging with impact on the sterile condition of the device,** the following principles should apply (see chart E):

Non-significant change:

- change of the sterilisation cycle parameters under the approved QMS;
- change of the shelf life validated by protocols approved by the notified body.

Significant change:

- change of sterilisation method, including changing a device from ‘non-sterile’ to ‘sterile’;
- changes in the design or packaging that adversely affect the sterility assurance or the effectiveness of the sterilisation (e.g. integrity of a seal).

Annex

Design changes and changes of the intended purpose which may be considered 'significant' when interpreting the first sentence of IVDR Art. 110(3) – Main Chart

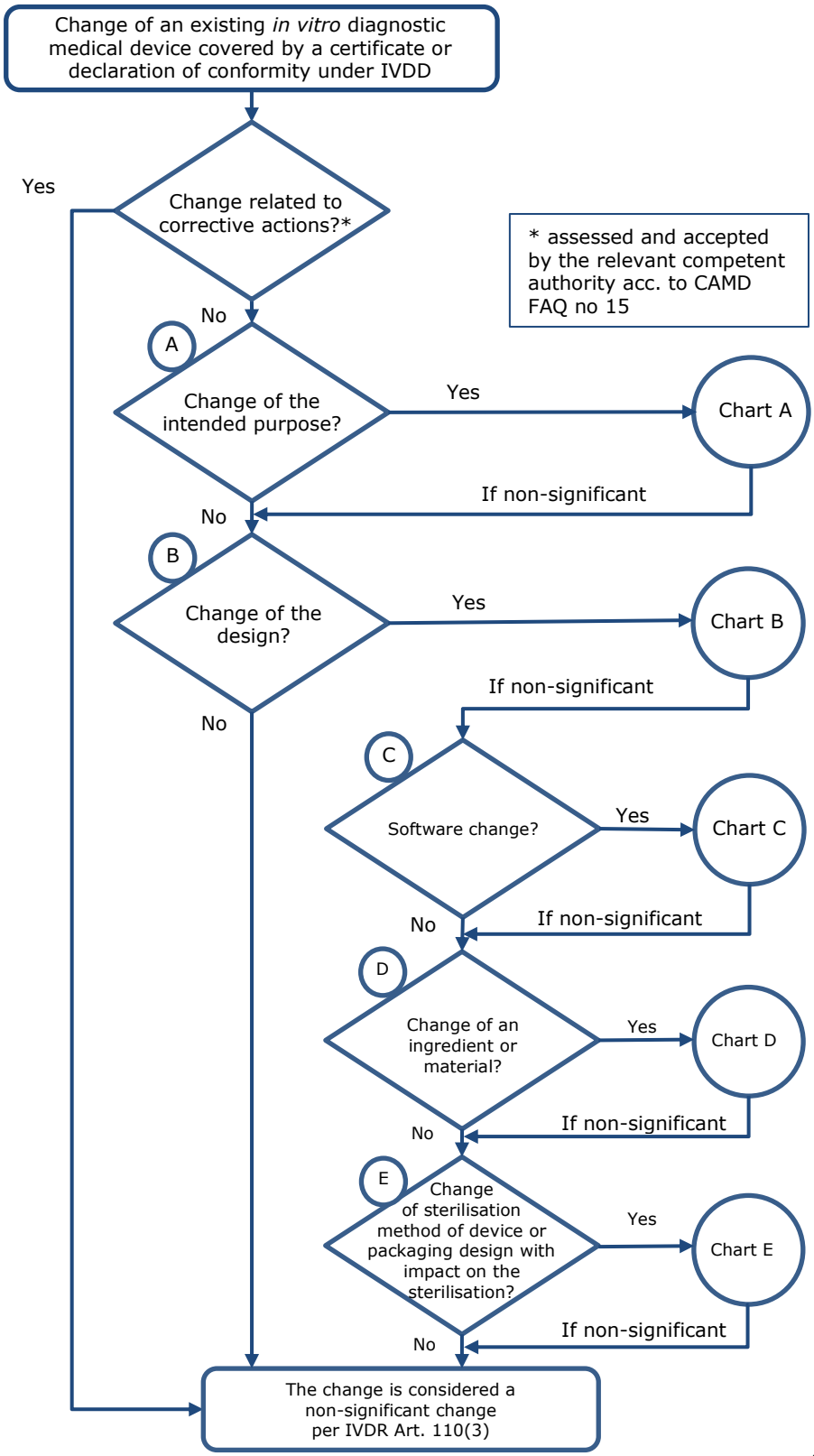


Chart A

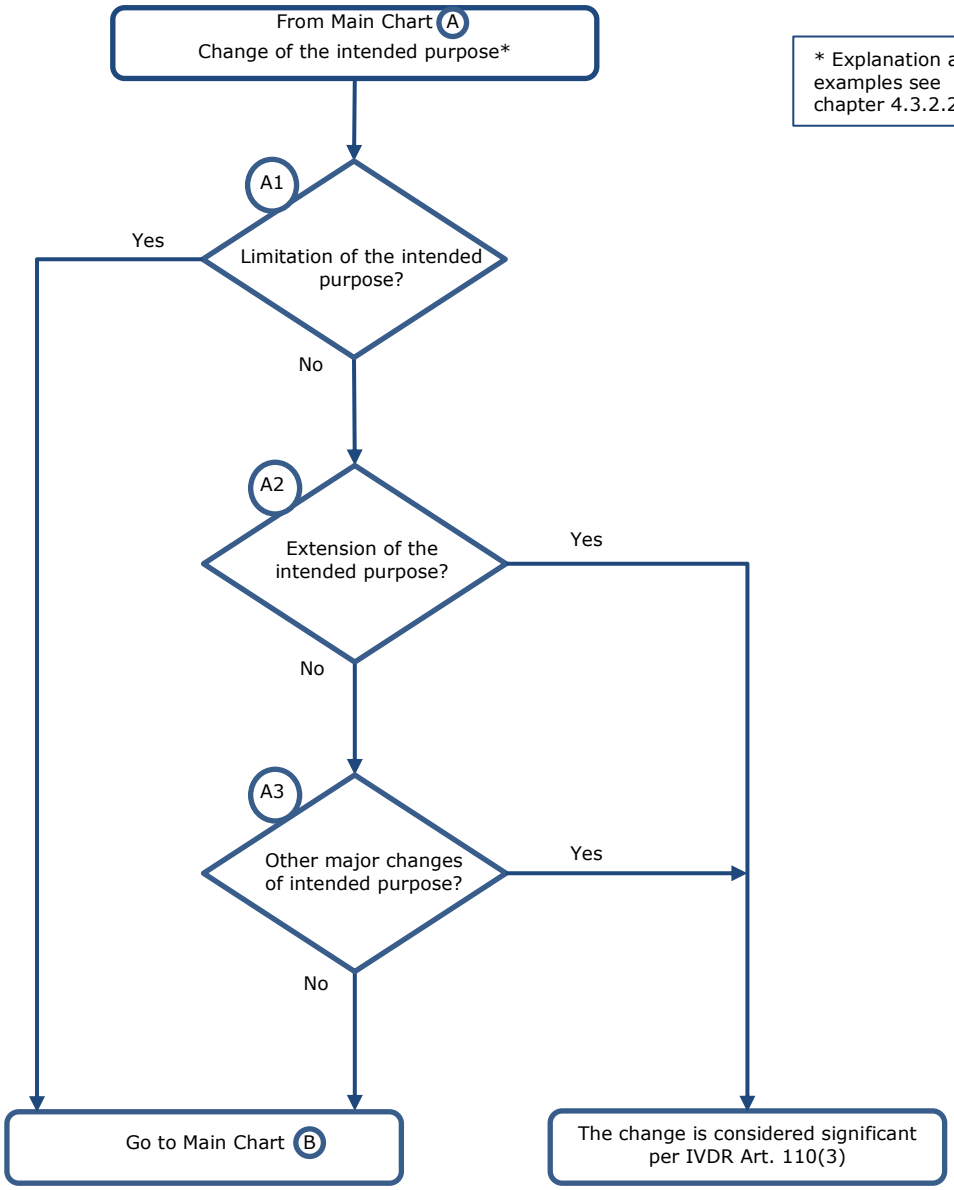

From Main Chart A
Change of the intended purpose*
* Explanation and examples see chapter 4.3.2.2.
A1
Limitation of the intended purpose?
Yes
No
A2
Extension of the intended purpose?
Yes
No
A3
Other major changes of intended purpose?
Yes
No
Go to Main Chart B
The change is considered significant per IVDR Art. 110(3)

Chart B

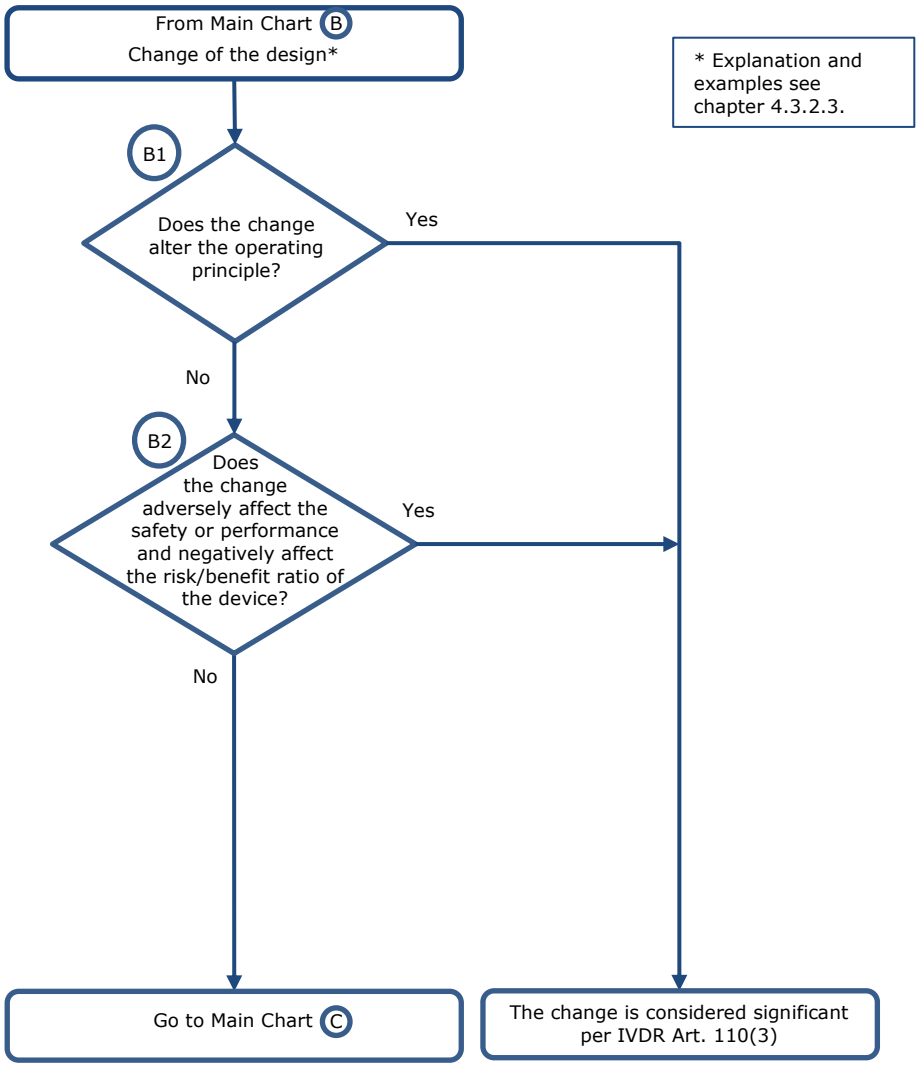

From Main Chart B
Change of the design*
* Explanation and examples see chapter 4.3.2.3.
B1
Does the change alter the operating principle?
Yes
No
B2
Does the change adversely affect the safety or performance and negatively affect the risk/benefit ratio of the device?
Yes
No
Go to Main Chart C
The change is considered significant per IVDR Art. 110(3)

Chart C

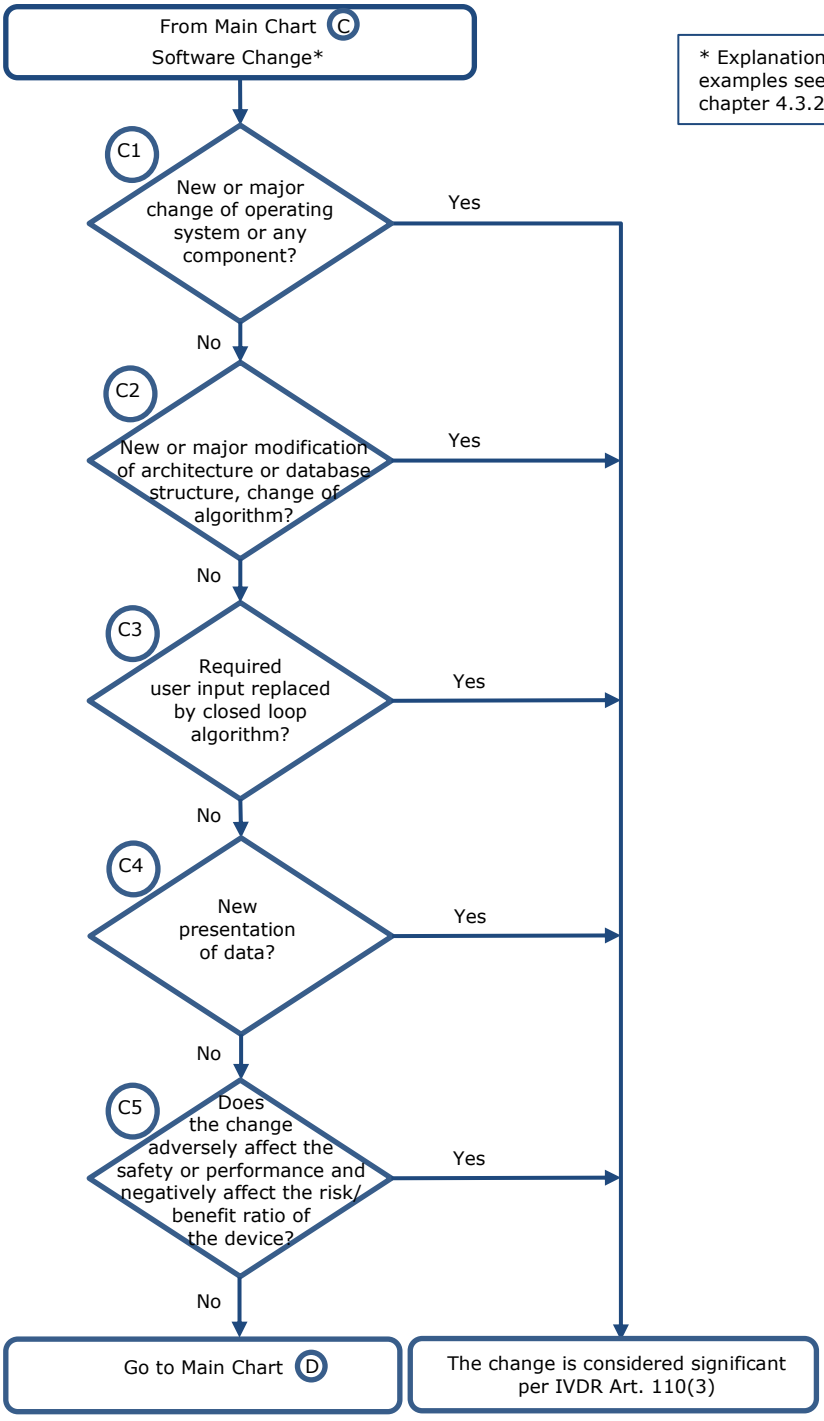

From Main Chart C
Software Change*
* Explanation and examples see chapter 4.3.2.3.
C1
New or major change of operating system or any component?
Yes
No
C2
New or major modification of architecture or database structure, change of algorithm?
Yes
No
C3
Required user input replaced by closed loop algorithm?
Yes
No
C4
New presentation of data?
Yes
No
C5
Does the change adversely affect the safety or performance and negatively affect the risk/ benefit ratio of the device?
Yes
No
Go to Main Chart D
The change is considered significant per IVDR Art. 110(3)

Chart D

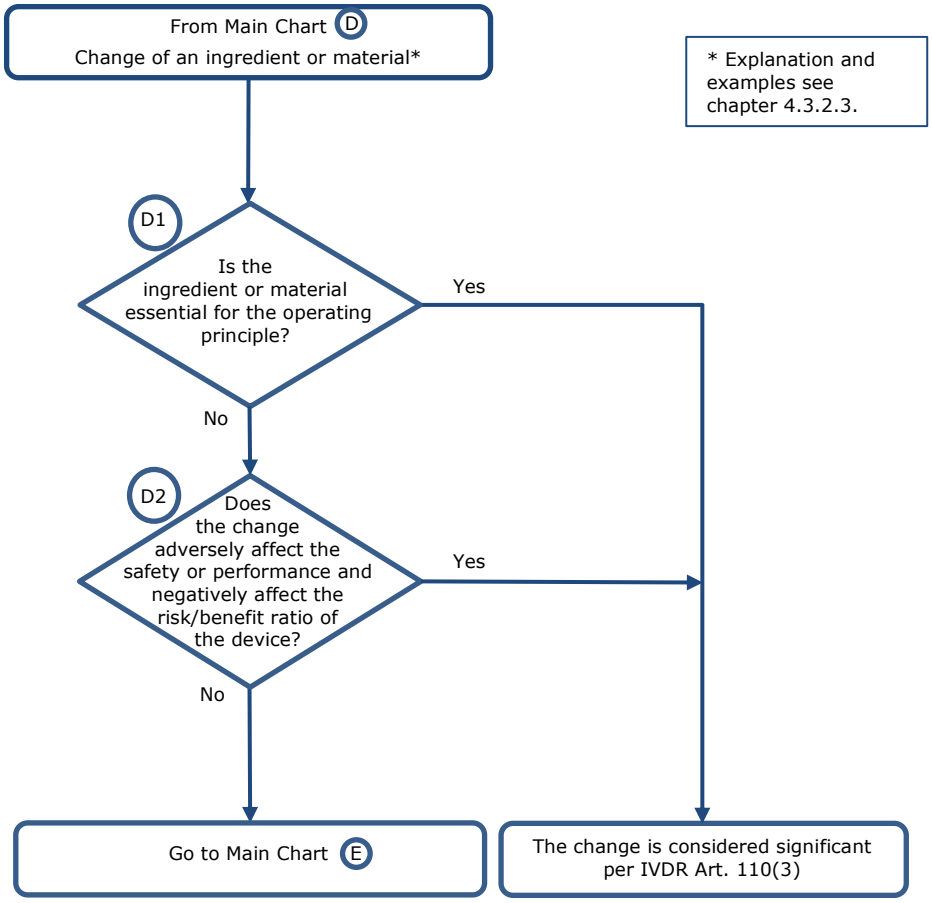
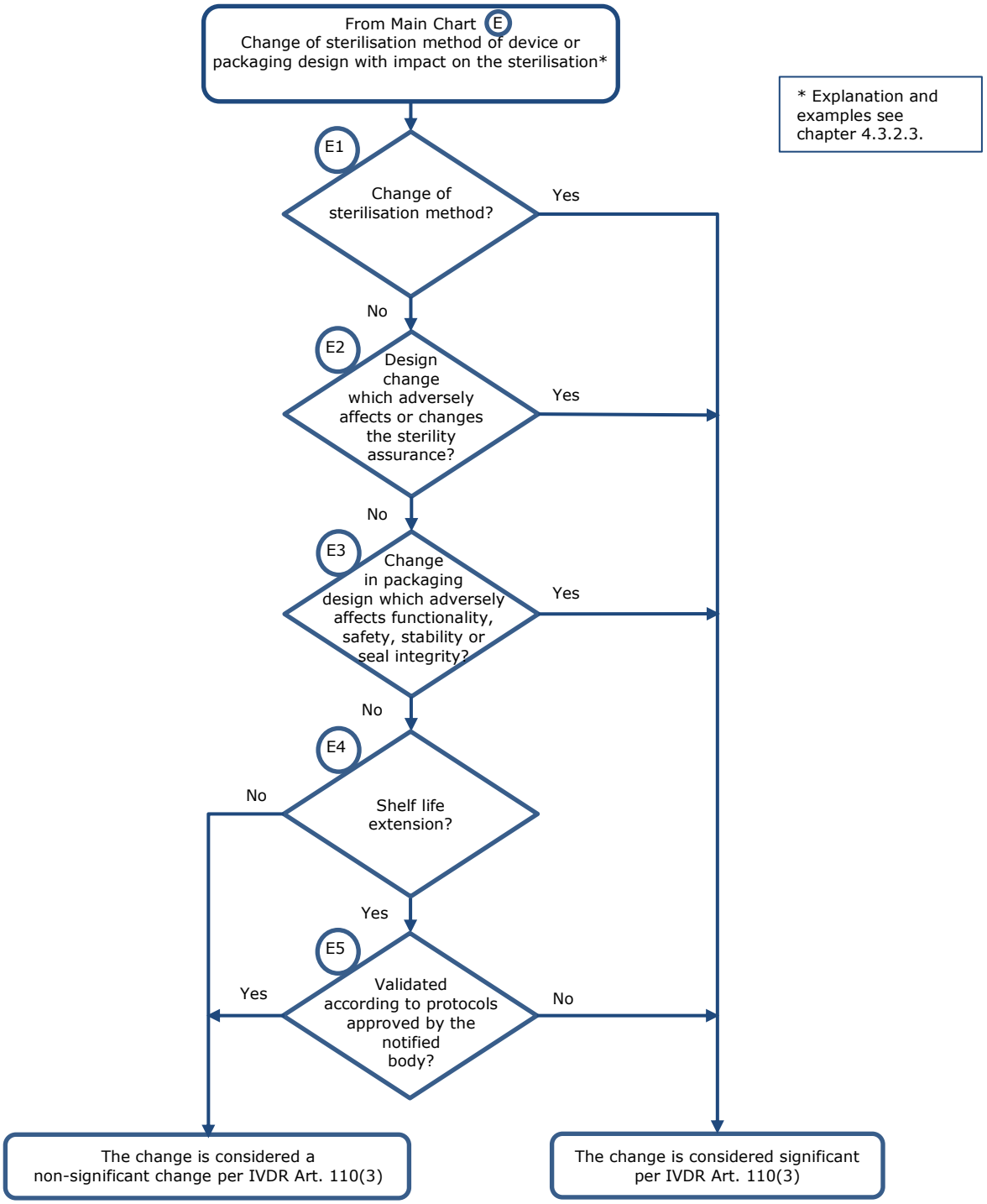

From Main Chart D
Change of an ingredient or material*
* Explanation and examples see chapter 4.3.2.3.
D1
Is the ingredient or material essential for the operating principle?
Yes
No
D2
Does the change adversely affect the safety or performance and negatively affect the risk/benefit ratio of the device?
Yes
No
Go to Main Chart E
The change is considered significant per IVDR Art. 110(3)

Chart E


From Main Chart E
Change of sterilisation method of device or packaging design with impact on the sterilisation*
* Explanation and examples see chapter 4.3.2.3.
E1
Change of sterilisation method?
Yes
No
E2
Design change which adversely affects or changes the sterility assurance?
Yes
No
E3
Change in packaging design which adversely affects functionality, safety, stability or seal integrity?
Yes
No
E4
Shelf life extension?
No
Yes
E5
Validated according to protocols approved by the notified body?
Yes
No
The change is considered a non-significant change per IVDR Art. 110(3)
The change is considered significant per IVDR Art. 110(3)