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Your Regulatory Partners for Devices, Diagnostics and Digital Health!

MEDTECH REGULATORY AFFAIRS CONSULTANCY





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EU AR / PRRC SERVICES

We can act as your PRRC or EU AR within the scope of the new EU Medical Device or IVD Regulations.

ABOUT US

Med-Di-Dia is a regulatory and quality compliance consultancy supporting Medical Devices, In-Vitro Diagnostics and Digital Health companies from our base in Galway, Ireland.

Our experts have 20+ years of experience in the medical industry who are passionate about supporting companies developing innovative technology for the benefit of patients and clinical teams.

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- EU and UK Market Access, opening doors to Rest of World
- Design History File - design controls and documentation
- Intended Purpose / Device Risk Classification
- Clinical Evaluation Reports (medical devices) / Performance Evaluation Reports (IVDs)

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

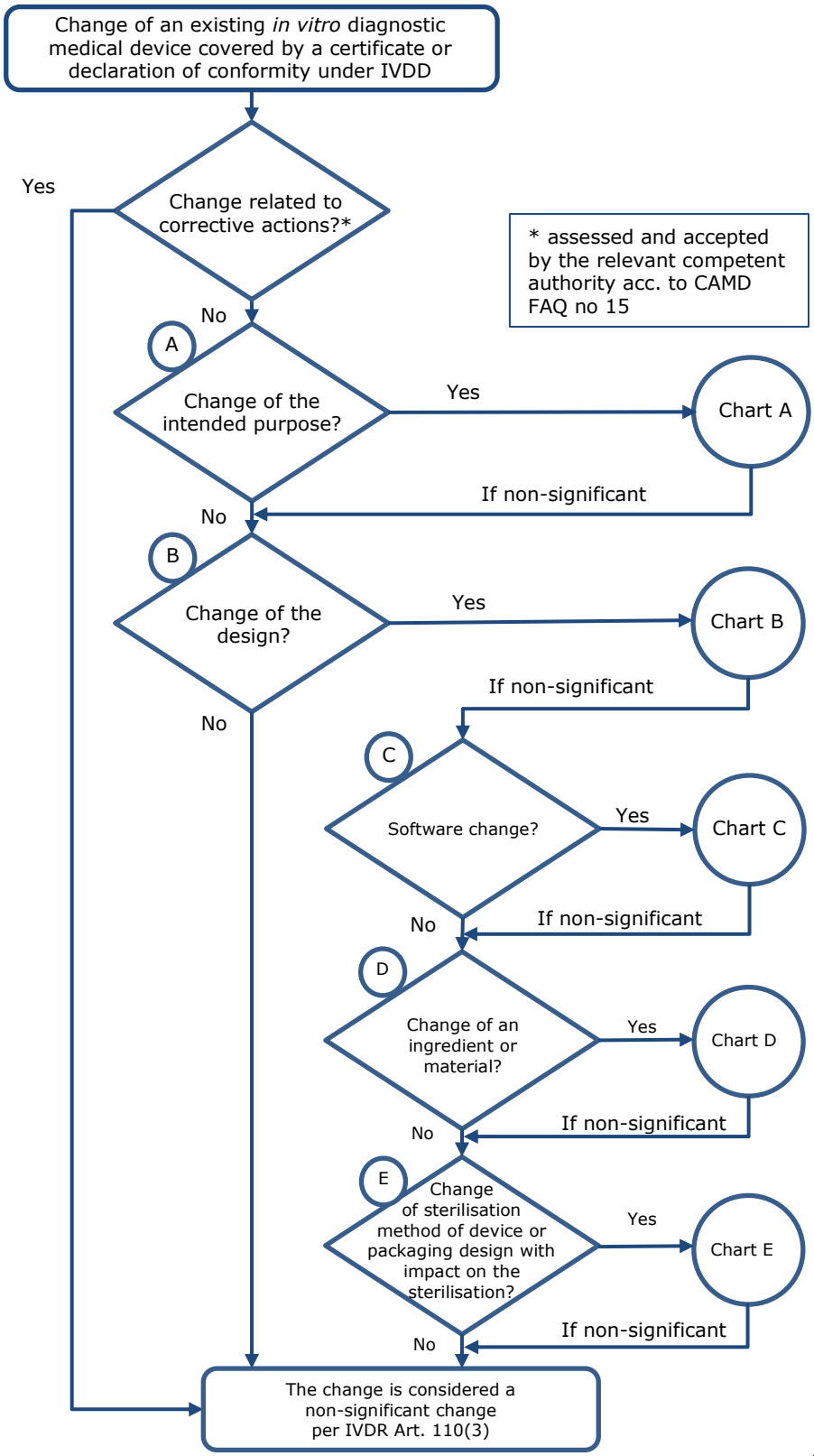


Chart A

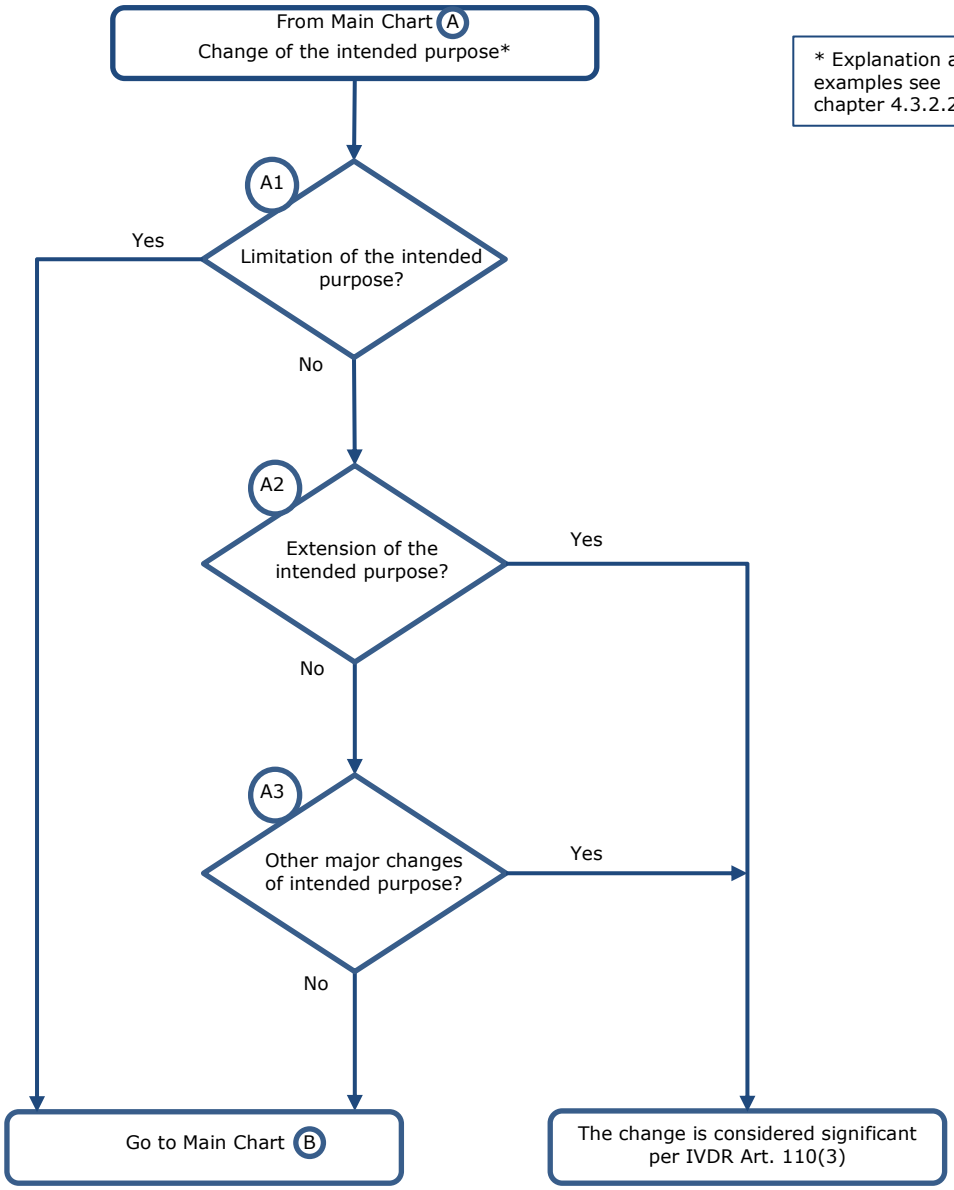

From Main Chart A
Change of the intended purpose*
* Explanation and examples see chapter 4.3.2.2.
A1
Limitation of the intended purpose?
Yes
No
A2
Extension of the intended purpose?
Yes
No
A3
Other major changes of intended purpose?
Yes
No
Go to Main Chart B
The change is considered significant per IVDR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

Chart B

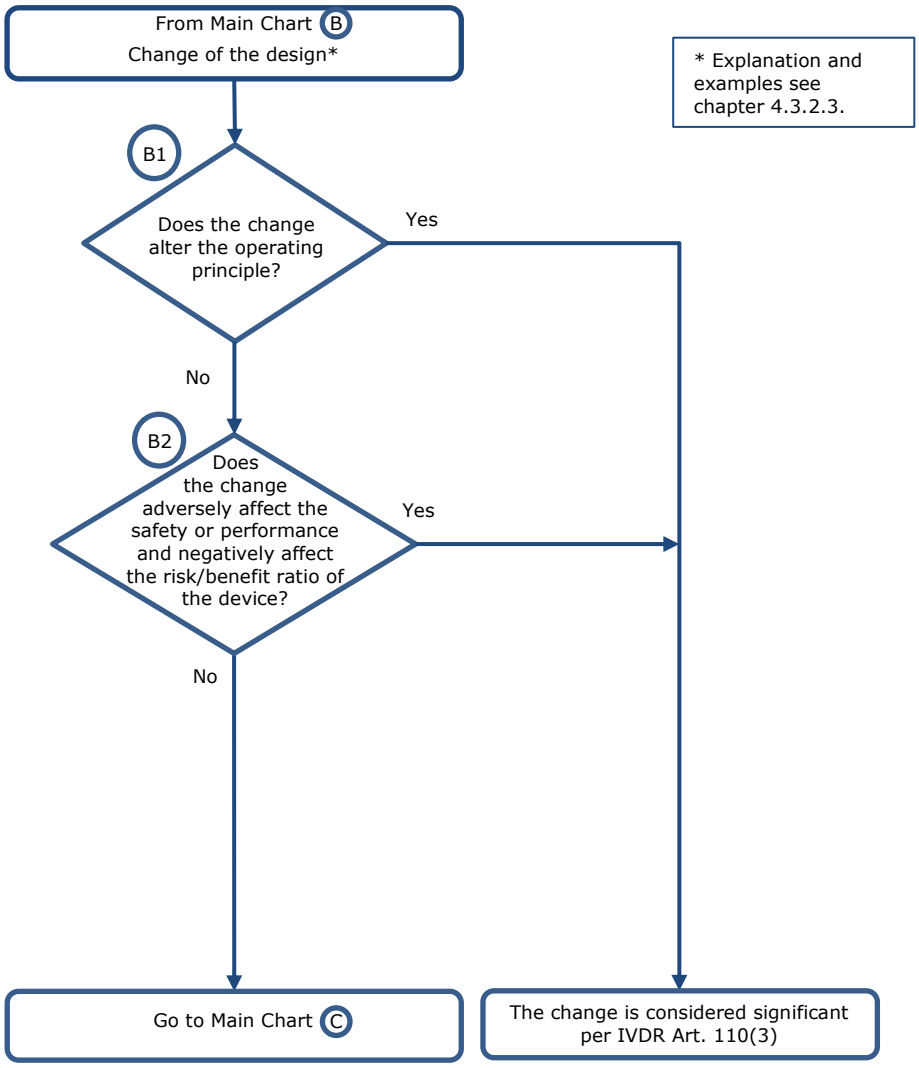

From Main Chart B
Change of the design*
* Explanation and examples see chapter 4.3.2.3.
B1
Does the change alter the operating principle?
Yes
No
B2
Does the change adversely affect the safety or performance and negatively affect the risk/benefit ratio of the device?
Yes
No
Go to Main Chart C
The change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

Chart C

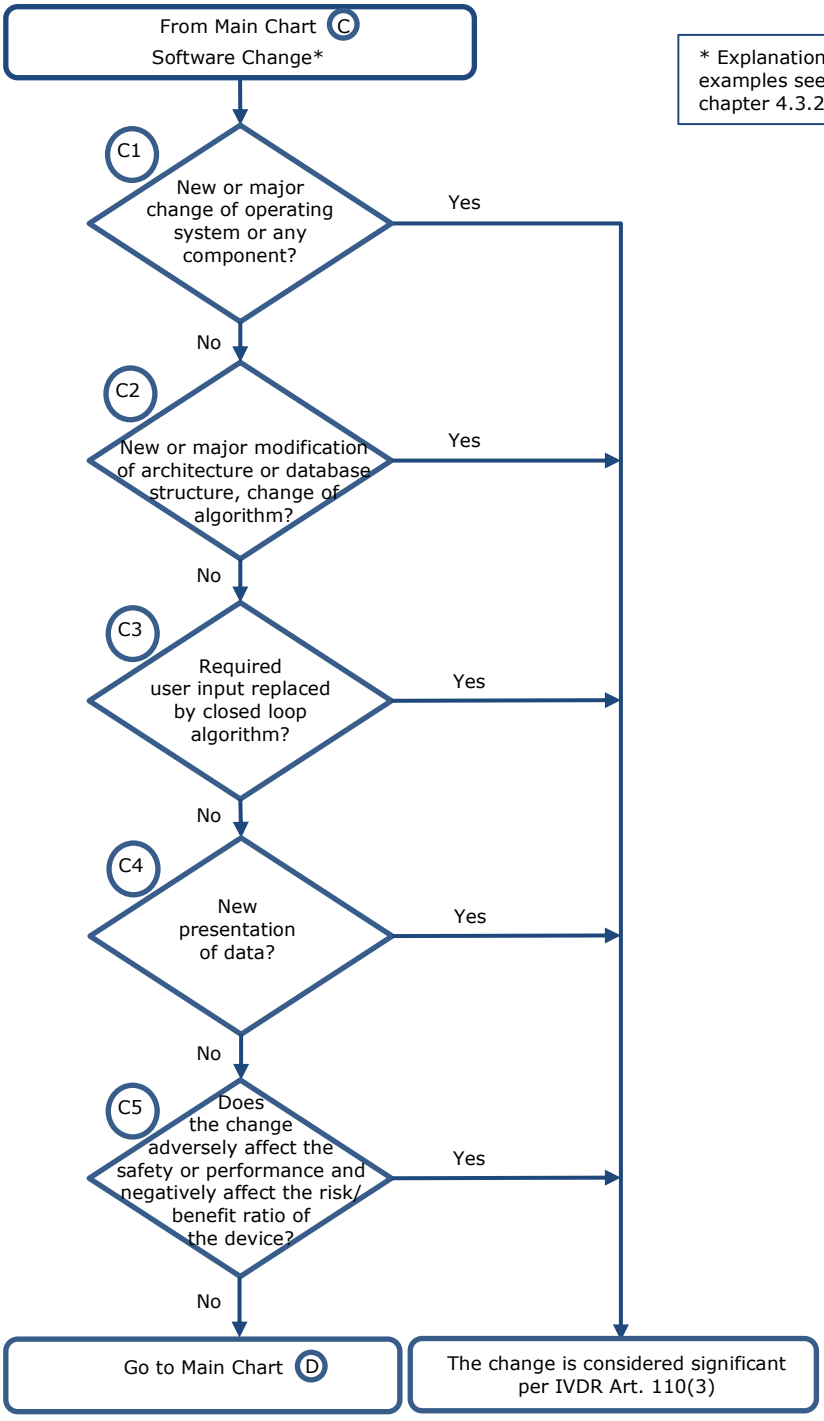

From Main Chart C
Software Change*
* Explanation and examples see chapter 4.3.2.3.
C1
New or major change of operating system or any component?
Yes
No
C2
New or major modification of architecture or database structure, change of algorithm?
Yes
No
C3
Required user input replaced by closed loop algorithm?
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

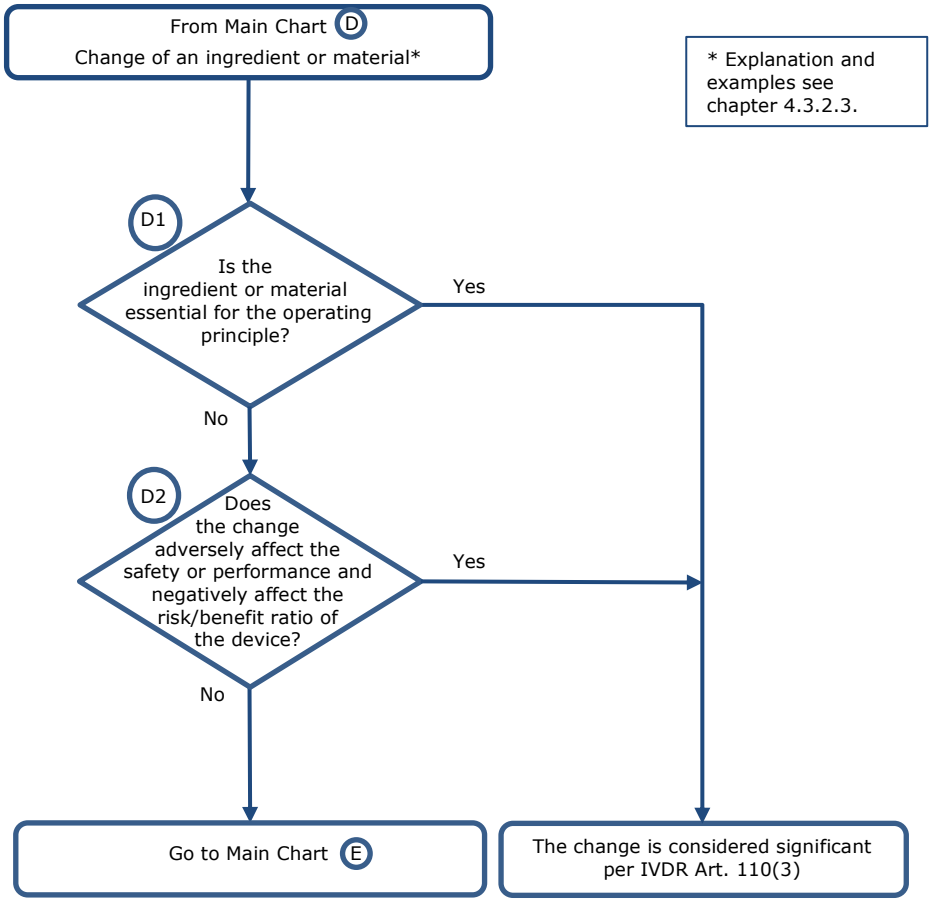
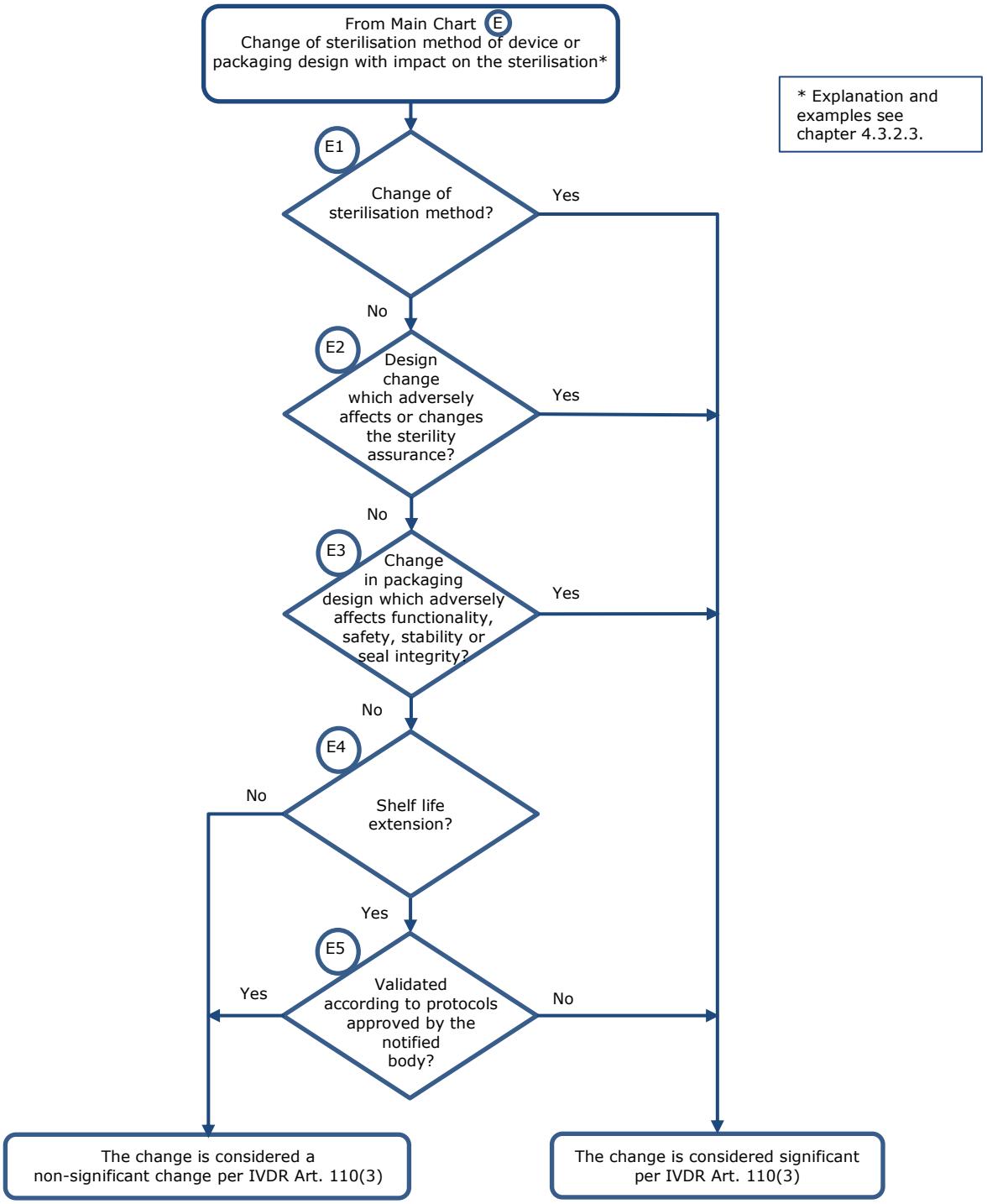

From Main Chart D
Change of an ingredient or material*
* Explanation and examples see chapter 4.3.2.3.
D1
Is the ingredient or material essential for the operating principle?
Yes
No
D2
Does the change adversely affect the safety or performance and negatively affect the risk/benefit ratio of the device?
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)

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