MDR requirements on hazardous substances

19 July 2019

[Version 2.0]

This document is being updated on a regular basis to reflect new insights and experience gathered by MedTech Europe members as they progress with the implementation of these requirements. Therefore, please consider this document as a work in progress and do not hesitate to contact the MTE Secretariat with suggestions to improve this guidance.

Introduction

Provisions on CMR (carcinogenic, mutagenic, reprotoxic) and ED (endocrine disrupting) substances can be found in Annex I ('General safety and performance requirements') of the Medical Devices Regulation (MDR)[1], in Chapter II ('Requirements regarding design and manufacture') and Chapter III ('Requirements regarding the information supplied with the device').

Some requirements are general with a focus on manufacture and design (Chapter II, Section 10.4.1.), while others lay out specific requirements, e.g. regarding the presence and justification of specific (CMR 1A/1B and ED) substances (Chapter II, Section 10.4.2.), labelling of certain devices (Chapter II, Section 10.4.5.) and inclusion of precautionary statements in the IFU (Instructions for Use) (Chapter III, Section 23.4. (s)).

MDR Annex I, Chapter I – General safety and performance requirements

All risk control measures related to substances should be embedded in the general risk management system as described in Section 3 of Chapter I, Annex I. For the overall risk assessment of a medical device, all substances of concern as specified in the MDR may need to be considered. However, for the specific requirements described below (e.g. Sections 10.4.1., 10.4.2., 10.4.5. and Section 23.4. (s)), the assessment may be more limited in scope in terms of the parts of the device and the subset of substances that needs to be considered.

State of the art practices for biocompatibility

The EN ISO 10993 series partly cover the MDR substances requirements, but do not fulfil them all. At the same time, these standards may be more detailed than the MDR on some other points.

For example, ISO 10993-3:2014 specifies strategies for risk estimation, selection of hazard identification tests and risk management, with respect to the possibility of potentially irreversible biological effects (genotoxicity; carcinogenicity; reproductive and developmental toxicity) arising from exposure to medical devices. It is applicable when the need to evaluate a medical device for potential genotoxicity, carcinogenicity, or reproductive toxicity has been established.

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1) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (Medical Devices Regulation)

Annex ZA of the EN standard for ISO 10993-3 correlates the MDD (Medical Devices Directive[2]) 'essential requirements' with the parts of the standard fulfilling those requirements. As no standards have been harmonised against the MDR yet, this is what is currently available.

MDR Annex I, Chapter II – Requirements regarding design and manufacture

10. Chemical, physical and biological properties

Section 10. contains general requirements on substances, of which Section 10.1. (a and b), Section 10.2. and Section 10.3. (***see Annex III of this guidance document for corresponding parts of the regulation***) are deemed relevant for the more specific requirements on CMR, ED and/or sensitising substances.

10.4. Substances

10.4.1. Design and manufacture of devices – General

See above: 'State of the art practices for biocompatibility'

10.4.1. Design and manufacture of devices – Specific (CMR 1A/1B and ED substances)

Scope of MDR Section 10.4. (CMR 1A/1B and ED)

In accordance with the flowchart in **Annex I to this document**, Section 10.4.1. defines the scope of the requirement as devices/parts/materials that meet one of the following criteria:

1) Invasive and come into direct contact with the human body;
2) (re)administer medicines, body liquids or other substances, including gases, to/from the body, or;
3) Transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body.

For criteria 1), this category covers only those devices, parts and materials that are both invasive and in direct physical contact with the patient. Parts of the device that do not make direct physical contact with the body are excluded.

For criteria 2) and 3), these categories cover only those parts or materials of the device that are in physical contact with the medicines, body liquids/fluids or other substances to be administered, re-administered, transported or stored.

2) Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

Rationale:

As the intent of the MDR is to protect the safety and health of the patient that might be exposed to hazardous substances present in the device materials, and as this goal is addressed by assessing the materials that can have direct physical contact with the medicines, body liquids/fluids or other substances to be administered or re-administered or transported or stored, criteria 2) and 3) cover only those device parts and materials used therein that are in physical contact with the medicines, body liquids/fluids or other substances.

For the devices/parts/materials determined to be in scope of the above criteria, Section 10.4.1. requires an assessment of the following substances:

- Substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B, in accordance with the harmonised classification in Annex VI of the CLP Regulation or;
- Substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified in accordance with the REACH or Biocidal Products Regulations.

Definition of '(re)administer' medicines, body liquids or other substances, included gases, to/from the body

In accordance with the MDR text, "administer medicines, body liquids or other substances", it is understood that "administering" means directing a medicine, body liquid or other substance **toward** the body. In Annex I, 7.5. of the Medical Devices Directive, the requirement was *"If parts of a device (or a device itself) intended to administer **and/or remove** medicines, body liquids or other substances to or from the body"*. Therefore, the decision to remove the wording "**and/or remove**" from the MDD text for the MDR text would indicate that removing substances is no longer in scope for the CMR/ED requirements, unless they are intended to be re-administered.

For example, wound dressings absorb fluids from the body. They are removing body fluids but do not administer any fluids to or from the body. The wound dressing would therefore be out of scope for the CMR/ED requirements under the MDR.

Definition of 'invasive'

The definition of 'invasive' in the MDR (Article 2(6)) is given as: "*any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body*".

This definition is the same as the definition in the MDD (Annex IX, 1.2). The MDD goes on to say that "*for the purposes of this Directive devices other than those referred to in the previous subparagraph and which produce penetration other than through an established body orifice, shall be treated as surgically invasive devices*". Therefore, anything invasive is either 'through body orifice' or 'surgically invasive'.

The definition in the MDR can be interpreted to include this clarifying sentence as well. This means that, for example, a treatment of a chronic wound (a breached epidermis could be considered 'through' the surface of the body) is neither surgically invasive nor it is through a body orifice. Therefore, it would not be considered 'invasive'.

Calculation of 0.1% w/w threshold for CMR 1A/1B and ED substances

Question/issue:

How to interpret the 0.1% w/w concentration threshold for hazardous substances in selected devices, parts and/or materials falling in scope of the MDR requirements (invasive etc.) in determining applicable obligations for device labelling and risk justification.

In accordance with the MDR text ("*Devices or those parts thereof or those materials used therein*"), the 0.1% threshold is clearly intended to apply not at an overall device level, but at the part and material level where such complexity exists.

Proposed solution:

1. Identify the device, those parts thereof or those materials used therein that are in scope of the hazardous substances requirement (***see flowchart in Annex I***).

   Note: Generally, the component in scope will be one material and calculation of the concentration of CMR/ED substances will be relatively easy. However, there may be more complex cases which are further explained in step 3.

2. Collect information on the presence of targeted substances in the devices, parts or materials identified in step

3. Assess the concentration of a targeted substance in the device, part or material. In the absence of an indication in the MDR text or related guidance document at this moment, it is left to the appreciation of each manufacturer to decide whether the assessment is to be performed in line with the REACH[3] approach on SVHCs in articles[4] or in line with the RoHS[5] approach on homogeneous materials. The chosen method may depend for example on the type of device, part or material undergoing the assessment (***see examples below***).

   Note: Further approaches may exist. The choice of the most adequate approach (REACH, RoHS or other) is to be made by the manufacturer.

   a. REACH approach on SVHCs in articles:
      - In the case of a device containing several components that are assembled or joined together, the concentration threshold will apply separately to each of those components that is considered an "article"[6] under REACH.
      - In the particular case of components to which a coating mixture (functional coating, sealant, solder etc.) is applied and forms a new coated "article", the concentration threshold will apply to the coated component ("article") and not to the component and coating material separately.

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3) Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH): https://echa.europa.eu/regulations/reach/legislation

4) See ECHA guidance on requirements for substances in articles: https://echa.europa.eu/regulations/reach/candidate-list-substances-in-articles

5) Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment: http://ec.europa.eu/environment/waste/rohs_eee/index_en.htm

6) REACH Article 3(3): "*an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition*"

- In cases where materials are not covered by the "article" definition/ approach (i.e. substances or mixtures as defined by REACH, like liquids/powders etc. applied on a component without becoming an integral part of the "article"), the concentration threshold will apply to such materials on their own.

b. RoHS approach on homogeneous materials:
   - In the case of a device containing several components that are assembled or joined together, the concentration threshold will apply separately to each of those components that is considered a "homogeneous material" under RoHS[7].
   - In the particular case of components to which a coating mixture (functional coating, sealant, solder etc.) is applied, the concentration threshold will apply to the component and coating material separately.

Rationale:

Only components (devices, parts or materials) in scope of the hazardous substances requirements should be considered for further assessment of the 0.1% threshold. For all other components, the general MDR provisions e.g. on risk assessment ensure that safety objectives are met for the device in its entirety.

Both the REACH and RoHS approach are considered well established and may be appropriate to assess the risk of patient or user exposure to the substance. The method chosen may be dependent on the type of device, material or part that is undergoing the assessment.

REACH:

- Due to the "once an article always an article" ruling by the ECJ in 2015, calculations at article level result in a very strict and detailed assessment.
- This approach for SVHCs is broadly applied and communicated for a large number of substances (> 180 SVHCs) in all product groups.

RoHS:

- Offers the most detailed assessment for heterogeneous articles (e.g. due to surface treatment/ coating), where the overall concentration may not be representative for the determination of patient exposure[8].
- Applied to a lower number of (10) substances in a specific product group (EEE, thus less relevant for all non-active medical devices).

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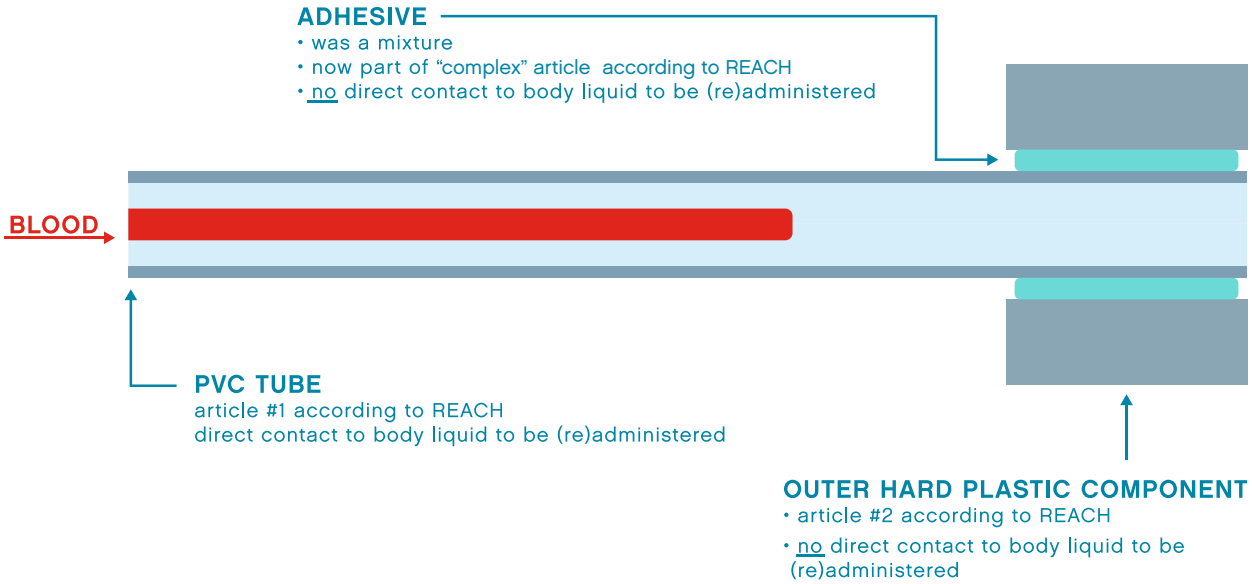
7) RoHS Article 3(20): "*one material of uniform composition throughout or a material, consisting of a combination of materials, that cannot be disjointed or separated into different materials by mechanical actions such as unscrewing, cutting, crushing, grinding and abrasive processes*"

8) For example, an invasive surgical blade is manufactured from a metal alloy and subsequently undergoes a coating process to apply a diamond coating protective layer. Under the REACH approach, the concentration threshold would apply to the final coated component and not to the metal alloy and coating material separately. Under the RoHS approach, the concentration threshold would apply to the metal alloy and coating materials separately.

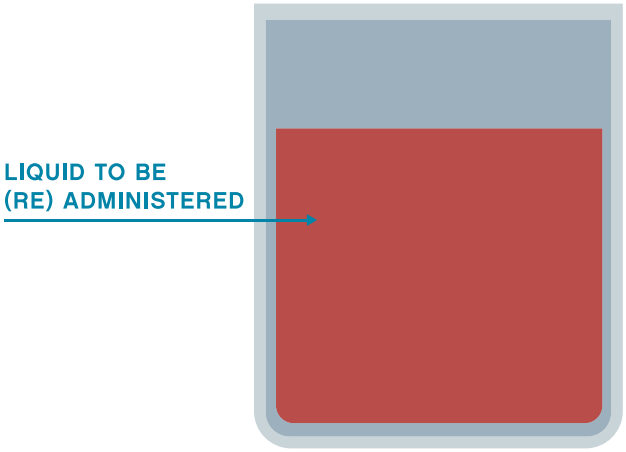
Example 1: Bloodline



Step 1: Identify the device, those parts thereof or those materials used therein that are in scope of the hazardous substances requirement.		**Step 2:** Collect information on the presence of targeted substances in the devices, parts or materials identified in step 1.	**Step 3:** Assess the concentration of a targeted substance in the device, part or material, using the REACH, RoHS (or another) approach.	
Component	In scope of MDR Section 10.4.? (assess using flowchart in Annex I)		To be assessed for MDR using REACH approach? (part is considered an 'article')	To be assessed for MDR using RoHS approach? (part is considered a 'homogeneous material')
Tube (#1)	Yes (direct contact)		Yes	Yes
Cured adhesive	No		NA	NA
Outer component (#2)	No (relevant part in contact with blood is already assessed on a more detailed level)		NA	NA
#1 + #2 + cured adhesive			NA	NA

NA: Not Applicable

Example 2: Multi-layer bag

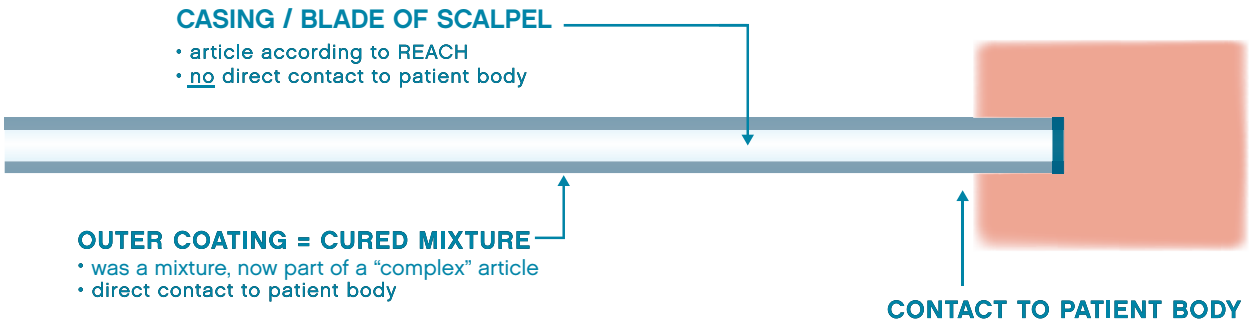


BAG CONSISTING OF SHEET + ADHESIVE + SHEET + OUTER PRINTING

Step 1: Identify the device, those parts thereof or those materials used therein that are in scope of the hazardous substances requirement.		**Step 2:** Collect information on the presence of targeted substances in the devices, parts or materials identified in step 1.	**Step 3:** Assess the concentration of a targeted substance in the device, part or material, using the REACH, RoHS (or another) approach.	
Component	In scope of MDR Section 10.4.? (assess using flowchart in Annex I)		To be assessed for MDR using REACH approach? (part is considered an 'article')	To be assessed for MDR using RoHS approach? (part is considered a 'homogeneous material')
Inner sheet (#1)	Yes (direct contact)		Yes	Yes
Cured adhesive	No		NA	NA
Outer sheet (#2)	No (no contact)		NA	NA
Sheets (#1 + #2)	No (two different 'articles'/'materials')		NA	NA
#1 + #2 + cured adhesive + cured ink	No (relevant part in contact with blood is already assessed on a more detailed level)		NA	NA

NA: Not Applicable

Example 3: Coated invasive device (e.g. casing of pacemaker)



Step 1: Identify the device, those parts thereof or those materials used therein that are in scope of the hazardous substances requirement.		**Step 2:** Collect information on the presence of targeted substances in the devices, parts or materials identified in step 1.	**Step 3:** Assess the concentration of a targeted substance in the device, part or material, using the REACH, RoHS (or another) approach.	
Component	In scope of MDR Section 10.4.? (assess using flowchart in Annex I)		To be assessed for MDR using REACH approach? (part is considered an 'article')	To be assessed for MDR using RoHS approach? (part is considered a 'homogeneous material')
Uncured coating mixture	No (not representative for relevant material, e.g. due to solvents)		NA	NA
Outer cured coating	TBD ('material' & direct contact) NB: most detailed level		No	Yes
Casing/blade…	No (no contact on its own; data could be input for the 2nd option)		NA	NA
Coated casing/…	TBD ('article' & direct contact) NB: Would also consider migration or body contact in case of incomplete/ damaged coating		Yes	No

NA: Not Applicable

Endocrine disruptors

Section 10.4.1. (b) defines two categories of endocrine disruptors: (i) those identified according to REACH Article 59, and (ii) those identified in accordance with the criteria established under the Biocidal Products Regulation 528/2012 ('BPR')[9].

This means that in view of this section, endocrine disruptors will be either identified through:

- The REACH procedure, applicable to all chemical substances. Substances identified on the REACH Candidate list as endocrine-disrupting substances for human health can be found on the ECHA website: https://echa.europa.eu/candidate-list-table[10].
- The BPR procedure (laid down in Commission Delegated Regulation (EU) 2017/2100), applicable to biocidal active substances and co-formulants[11]. No publicly available list/search function is available (yet) for substances which have been identified as endocrine disruptors under the BPR.

This second category of endocrine disruptors applies to substances identified as endocrine disruptors to human health under the Biocidal Products Regulation and which are used in medical devices, whether as biocidal active substances or non-biocidal active substances.

For the purpose of compliance with Section 10.4. (i.e. risk justification and labelling), all other chemical substances can only be identified as endocrine disruptors under the REACH framework and related procedures.

Note: The EU regulatory framework on endocrine disruptors is still being defined. MedTech Europe will update its guidance in line with these developments.

10.4.2. Justification

The flowchart in Annex II suggests a flow of actions/assessments to be undertaken by a medical device manufacturer, which will either result in justification of the presence of a CMR 1A/1B and/or endocrine-disrupting (ED) substance or its substitution, in view of compliance with Section 10.4.2. The flowchart and the description below follow the legal text of Section 10.4.2., points a, b, and c.

The flowchart and guidance do not distinguish between the general patient population and patient groups which may be particularly vulnerable to certain substances and/or materials. Any benefit-risk assessment will have to address vulnerable patient groups as relevant for specific medical device applications. The MDR specifically calls out children and pregnant or breastfeeding women as patient groups that may be considered particularly vulnerable.

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9) Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products

10) To look for all endocrine disruptors for human health, filter the list by 'reason for inclusion': Endocrine disrupting properties (Article 57(f) – human health))

11) MDR Section 10.4.1. (b) states: "*[...] once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council, in accordance with the criteria that are relevant to human health amongst the criteria established therein.*" This delegated act is Commission Delegated Regulation (EU) 2017/2100, setting out scientific criteria for the determination of endocrine-disrupting properties. The criteria in this delegated act are not limited to active substances and apply to all substances assessed within the framework of the Biocidal Products Regulation, including co-formulants.

In addition to points a, b, and c, the medical device manufacturer, where applicable and available, needs to base the justification on "*the latest relevant scientific committee guidelines in accordance with Sections 10.4.3. and 10.4.4.*" (point d). Guidelines on phthalates in accordance with Section 10.4.3. will become available in 2019. A preliminary version of the guidelines was published in March 2019[12]. These preliminary guidelines suggest that "*[t]he approach of these Guidelines may also be used for a BRA [benefit-risk assessment] of other CMR/ED substances present in medical devices.*" This means that the final guidelines could apply to all CMR 1A/1B and endocrine-disrupting substances and no other guidelines in accordance with Section 10.4.4. would need to be developed.

Note: The guidance below is provided to medical device manufacturers in anticipation of the final scientific committee (SCHEER) guidelines and may change depending on the final version of the SCHEER guidelines. The preliminary SCHEER guidelines follow a very similar approach as described below for the analysis of exposure (toxicological risk assessment) under (a) but are more prescriptive on the analysis of alternatives under (b) and the benefit-risk assessment under (c), the latter in particular with regard to the assessment of the clinical benefit. Moreover, the preliminary SCHEER guidelines require a detailed uncertainty analysis which is not covered in the industry guidance below.

a) Analysis of exposure

After establishing that an invasive material, component, or finished device contains a CMR 1A/1B and/or ED substance at > 0.1% (w/w) per Section 10.4.1., an analysis to establish the potential patient or user exposure to the substance(s) is needed per Section 10.4.2. (a). This assessment is one part of a toxicological risk assessment that is used to determine if the exposure to the substance(s) is safe when considering benefit-risk ratios in Section 10.4.2. (c). A toxicological risk assessment (NRC, 1983; NAS, 1994) consists of four parts:

- **Hazard identification**: Identify the hazard(s) associated with the specific substance(s) present at > 0.1% (w/w). The hazard(s) should correlate with the classification of the substance (CMR 1A/1B and/or ED) as well as the biological safety data (i.e., toxicity data) that will be needed to determine if the exposure is safe. Document this information as the first part of the risk assessment.
- **Exposure assessment**: Estimate or measure through analytical chemistry the patient/user exposure. Because the % (w/w) value of a substance(s) is known, a worst-case exposure can be calculated using conservative assumptions (e.g., all of the substance(s) leaches from the material, component, or finished device) or information present in the scientific literature regarding the leaching rate of the substance(s) from a specific material. When a more refined assessment is preferred, the actual mass of the substance(s) that is extractable or leaches from a material, component, or finished device can be measured via a non-volatile residue approach[13] (see USP <661>) or extractables and leachables testing (see ISO 10993-12 and -18). In either case, document the daily dose (i.e., mg/day) of the patient/user exposure to the substance(s).

12) SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Preliminary version of the Guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties, 15 March 2019: https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_015.pdf
13) Assuming that the total NVR mass is the hazardous substance of interest.

- **Dose-response (toxicity) assessment**: Search the scientific literature, regulatory agency publications, and chemical databases (e.g., ECHA, EPA IRIS, ATSDR) for toxicity studies which define safe and unsafe levels of exposure, i.e., no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs). Consider the route, frequency, and duration of exposure when selecting data. The identified NOAEL/LOAEL values should be used by a trained professional to derive and document the tolerable exposure (mg/day) to the substance(s) (see ISO 10993-17).

- **Risk characterisation**: Bring all the information collected in the three prior steps together to determine the risk to the patient/user in a quantitative or, where this may not be possible, a qualitative manner. When the exposure is to a single substance, a margin-of-safety can be calculated by dividing the tolerable exposure by the daily dose. Toxicologists, risk assessors, and government regulators recognise that a margin-of-safety greater than 1.0 is indicative of individual chemical safety. When the exposure is to multiple substances, a hazard index can be calculated, which is the sum of the hazard quotients (i.e., inverse of the margin-of-safety) for each substance[14]. The hazard index should pertain to substances with a common toxicological mechanism or endpoint. That is, a hazard index for mutagenic substances would be distinct from that for reprotoxic substances and, in turn, multiple hazard indices may be required depending on the chemical composition of the exposure. A hazard index less than 1.0 is indicative of collective chemical safety. If a margin-of-safety or hazard index cannot be calculated, qualitatively characterise the risk using expert judgement. Document the conclusions of the risk characterisation and the impact to patient/user safety to complete the risk assessment.

b) Analysis of alternatives[15]

Create a list of possible alternative substances, materials or designs for the specific medical application based on knowledge from experts skilled in the art and science including published peer reviewed literature (including independent research, peer-reviewed studies and scientific opinions from relevant scientific committees).

c) Benefit-risk assessment

For the benefit-risk assessment, evaluate whether a substance and/or material substitution may be appropriate or not, and clarify the feasibility of a material change. This process consists of five points of consideration. These will guide the manufacturer in establishing the appropriateness of a possible substance and/or material substitution. Evaluate the substance and/or material substitute of the medical device by comparing it with the existing substance and/or material in regard to:

1. **Material properties**: Identify whether the substance and/or material to be replaced directly influences the relevant material properties. Material properties are relevant if they relate to the device performance, which should not be impaired. Performance aspects may include: ability to be reprocessed and sterilised, stability during application, fatigue resistance, or wear behaviour. For example, a polymeric reusable instrument should be adequately resistant to reprocessing (cleaning and sterilisation).

14) HI = HQ1 + HQ2 + HQ3…(with HQ = 1/MOS)

15) This part of the assessment may go beyond the expertise of a risk assessor and would most likely be best conducted by a materials scientist or R&D engineer.

2. **Functionality**: The substance and/or material substitution should not impair the functionality of the device. For example, for a screw driver, the torque momentum after material substitution should fulfil the same design requirements.

3. **Biological and clinical performance**: The substance and/or material change should not impair the established biocompatibility and/or clinical performance of the device. For example, a bearing device manufactured from CoCr and substituted with a titanium alloy may not be suitable due to inappropriate wear resistance potentially leading to an adverse tissue reaction.

4. **Supply/manufacturability**: The substance and/or material substitute should be available in amounts allowing adequate coverage of the clinical demand.

If one of the above considerations is unfavourable or does not meet minimum requirements, it is sufficient to provide a justification including the findings from the assessment above.

If all of the above considerations are favourable, perform a benefit-risk analysis with the substance and/or material substitute.

5. **Benefit-risk analysis**: The benefit-risk ratio[16] of the device containing the alternative substance and/or material substitute should be compared with the current device containing the CMR 1A/1B or ED substance. If the benefit-risk ratio of the current device is worse or equivalent to the device with the alternative substance and/or material substitute, a plan needs to be developed to substitute the CMR 1A/1B/ED substance and/or CMR 1A/1B/ED-containing material. If the benefit-risk ratio of the current device is better than the device with the alternative substance and/or material substitute, no substitution needs to be done, and providing a justification including all the findings above is sufficient.

Note: The outcome of the benefit-risk assessment can differ for an existing product versus a new product that is still under development.

<u>References on risk assessment</u>

- EN ISO 14971:2012: Medical devices - Application of risk management to medical devices.
- ISO 10993-12:2012. Biological evaluation of medical devices—Part 12: Sample preparation and reference materials.
- ISO 10993-17:2008. Biological evaluation of medical devices—Part 17: Establishment of allowable limits for leachable substances.
- ISO 10993-18:2005. Biological evaluation of medical devices—Part 18: Chemical characterization of materials.
- National Academy of Science. Science and Judgment in Risk Assessment. Washington, D.C.: National Academy Press, 1994.
- National Research Council. Risk Assessment in the Federal government: Managing the Process. Washington, D.C.: National Academy Press, 1983.
- United States Pharmacopeia Chapter <661>, Plastic Packaging Systems and Their Materials of Construction, USP41-NF36.

16) The benefit-risk ratio is not necessarily a quantitative value but can be the qualititative conclusion of the benefit-risk assessment (see EN ISO 14971).

10.4.5. Labelling

Note: This chapter only covers the requirements of MDR Sections 10.4.5. and 23.2. (f) related to identifying the presence of CMR 1A/1B and/or endocrine disrupting substances. It does NOT cover precautions in the Instructions for Use that may be required according to MDR Section 23.4. (s), which is covered in the next chapter of this guidance.

MedTech Europe identified two main options to label and identify CMR 1A/1B and/or ED substances present in medical devices or parts or materials thereof. Option 2 follows a literal reading of Section 10.4.5. to list the substance(s) on the label. Option 1 is based on MDR Annex I, Chapter III, Section 23.1. (h), which allows the use of symbols on the label as an alternative to written language.

Medical devices need to fulfil the labelling requirement to comply with the Medical Device Regulation. The date of application of the MDR is 26 May 2020, however the 'grace period' allows that certain devices can still be CE-marked under the Medical Device Directive after that date. In that case, as long as the certificates for those devices are valid and until May 2024 at the latest, they would need to follow the provisions on hazardous substances in the Directive, which only requires labelling and risk justification for phthalates but not for other CMR 1A/1B and/or ED substances.

Option 1: Use of symbol on the label & identification of the substance(s) in the IFU[17]

The first option for labelling CMR 1A/1B and/or endocrine disrupting substances is to include the below symbol (proposed for inclusion in the revised ISO 15223-1 standard) on the label. This option requires that the symbol is accompanied by a description in the IFU until the symbol has been harmonised against the MDR. Moreover, the MDR requires that each CMR 1A/1B or endocrine disrupting substance present in a device, a part of material thereof is identified individually. Therefore, this option requires that the substance(s) is/are listed in the IFU, in addition to including the symbol on the label (on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging).

Label:

To indicate the presence of (a) CMR 1A/1B and/or endocrine disrupting substance(s) (= substances referred to in points (a) or (b) of MDR Section 10.4.1.) present in the medical device (or parts or materials thereof) in a concentration above 0.1% weight by weight (w/w), a manufacturer may choose to add the following symbol to the label:

This symbol will become part of the revised ISO 15223-1 standard, which is expected to be published at the beginning of 2020. The symbol may also become harmonised against the MDR, which could happen in 2021 at the earliest.

17) Or in the documentation supplied with the device for devices which may not have an IFU.

Note: Further guidance on MDR symbols is available in MedTech Europe's industry guidance on "Use of symbols to indicate compliance with the MDR"[18].

Instructions for Use:

1. Until the symbol has been harmonised against the MDR[19], it needs to be described in the IFU. This can be done by using the title and/or the description of the symbol as indicated in the ISO 15223-1 standard:

   Title: "*Contains hazardous substances*"

   Description: ''*Indicates a medical device that contains substances that can be carcinogenic, mutagenic, reprotoxic (CMR), or substances with endocrine disrupting properties.*''

   This description is part of the IFU section that provides information on all symbols used.

2. In addition to adding the symbol to the label (which by itself is not sufficient to comply with Section 10.4.5.), the CMR 1A/1B and/or endocrine disrupting substance(s) present in the medical device (or parts or materials thereof) in a concentration above 0.1% w/w will need to be identified by listing the substance(s) in the IFU.

   The legal text suggests that the substance name needs to be provided. Manufacturers may however consider other identifiers, e.g. established numbering systems such as CAS and/or EC (see Option 2 for various options to list substances).

   It is recommended to include a link to the ECHA homepage[20], where users will be able to find more information about the substance, especially if a numbering system is used.

   Manufacturers should ensure that any reference(s) used to list the substance(s) (whether substance name, CAS/EC number or other identifier) provide(s) a unique identifier for the substance(s) present in the device.

   Furthermore, it is suggested to also inform users of the reasons why the substance(s) is/are labelled, i.e. because they are classified as CMR 1A/1B and/or endocrine disrupting substance(s) and because they are present in a concentration above 0.1% weight by weight.

   Example:

   This device [or: one or more components of this device[21]] contains the following substance(s) defined as CMR 1A and/or CMR 1B and/or endocrine disrupting substances[22] in a concentration above 0.1% weight by weight:

   • Bis(2-ethylhexyl) phthalate; CAS No.: 117-81-7; EC No.: 204-211-0
   • Lead; CAS No.: 7439-92-1; EC No.: 231-100-4

18) https://www.medtecheurope.org/resource-library/use-of-symbols-to-indicate-compliance-with-the-mdr/

19) See MDR Annex I, Chapter III, Section 23.1. (h): "Where appropriate, the information supplied by the manufacturer shall take the form of internationally recognised symbols. Any symbol or identification colour used shall conform to the harmonised standards or CS. In areas for which no harmonised standards or CS exist, the symbols and colours shall be described in the documentation supplied with the device."

20) https://echa.europa.eu/home

21) Manufacturer to choose the option that is most relevant. This does not necessarily mean that the specific component(s) need(s) to be identified.

22) Statement can be further adjusted to list only the classification(s) of the substance(s) present. E.g. for DEHP this would be reprotoxic 1B (or CMR 1B) and endocrine disrupting.

This information (substance identification) can be part of the precautions/warnings section of the IFU. It will enable the user to look up additional information about the substance(s), e.g. by using the chemical search on the ECHA website.

Option 2: Listing of substance(s) on the label & additional information in the IFU

Label:

Alternatively to using the symbol, a manufacturer may list the CMR 1A/1B and/or endocrine disrupting substance(s) present in the medical device (or parts or materials thereof) in a concentration above 0.1% w/w on the label.

The MDR text does not specify how this needs to be done, it only requires the substance(s) to be listed:

- on the device itself and/or
- on the packaging for each unit or
- where appropriate, on the sales packaging.

The legal text suggests that the substance name needs to be provided. Manufacturers may however consider other identifiers, e.g. established numbering systems such as CAS and/or EC.

It is recommended to include a link to the ECHA homepage[23], where users will be able to find more information about the substance, especially if a numbering system is used.

Various options to list substances exist, for example[24]:

Substance identification	Examples
Substance name(s)	• Lead • Bis(2-ethylhexyl) phthalate
CAS number(s)	• CAS 7439-92-1 • CAS 117-81-7
EC number(s)	• EC 231-100-4 • EC 204-211-0
IUPAC name(s)	• LEAD or Lead Metal or Lead Metal Pb etc. • Bis (2-ethylhexyl)phthalate (DEHP) or Bis (2-ethylhexyl) Phthalate etc.
Internationally recognised chemical symbol(s)	• Pb • [Not applicable]
Other agreed abbreviation	• [Not applicable] • DEHP

23) https://echa.europa.eu/home

24) The information that will need to be submitted in EUDAMED is as follows (information available as of May 2019, to be confirmed in final EUDAMED specifications) (multiple entries are possible):
- Substance type (CMR or endocrine disrupting substance)
- For CMR substances: CMR type: CMR 1A or 1B
- Substance name (if the CAS or EC number is provided, the manufacturer does not additionally have to provide the substance name)
- CAS or EC number (at least one of both required for CMR substances, can be left blank for ED substances if no CAS and no EC number are available)
The substance name will not have to be translated for CMR substances as these are available in English in the ECHA database. For endocrine disrupting substances translation may be needed.
For the most recent information on EUDAMED, please refer to: https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/eudamed_en

Manufacturers may choose 1 or a combination of these different options, but should ensure that the reference(s) used to list the substance(s) (whether substance name, CAS/EC number or other identifier) allow unique identification of the substance(s) present in the device.

Instructions for Use:

If the substance(s) present is/are clearly identified on the label, no further information on the identity of the chemicals may be required in the Instructions for Use.

However, MedTech Europe recommends that manufacturers include a statement to inform users of the reasons why the substance(s) is/are labelled, i.e. because they are classified as CMR 1A/1B and/or endocrine disrupting substance(s) and because they are present in a concentration above 0.1% weight by weight (see example statement in Option 1).

MDR Annex I, Chapter III – Requirements regarding information supplied with the device

23.4. (s) Information in the instruction for use – All devices

Question/issue:

What approach will be taken to implement Section 23.4. (s)?

Proposed solution:

For precautions related to CMR and ED substances, manufacturers should consider the output of assessments done in accordance with Section 10.4.2. (risk justification) and Section 10.4.5. (labelling) regarding any residual risks and/or precautions that need to be disclosed in accordance with this section.

Manufacturers need to ensure and to document that their biocompatibility assessment covers the requirements of Section 23.4. (s) completely, considering:

- All the parts of the medical device that are directly or indirectly[25] in contact with the patient (implanted or non-implanted device) and/or user (for example latex gloves);
- All the CMR and ED substances that are referred to in this section.

When there is potential exposure to these substances (below relevant effect levels), and no additional precautionary statements are required for regular patients, manufacturers have to consider if precautionary statements are required for vulnerable patient groups (to meet Section 10.4.5.).

25) E.g. devices that channel or store substances that will eventually be administered to the body.

Disclaimer

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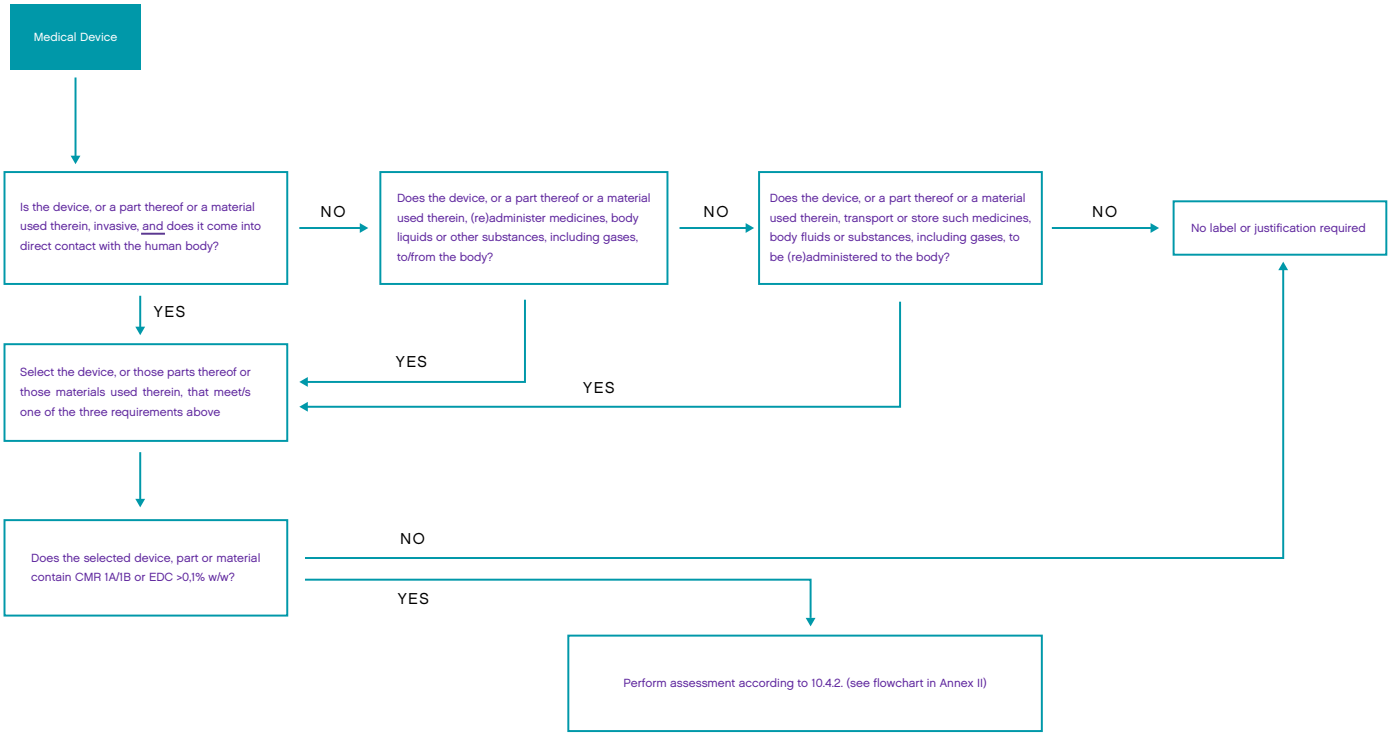
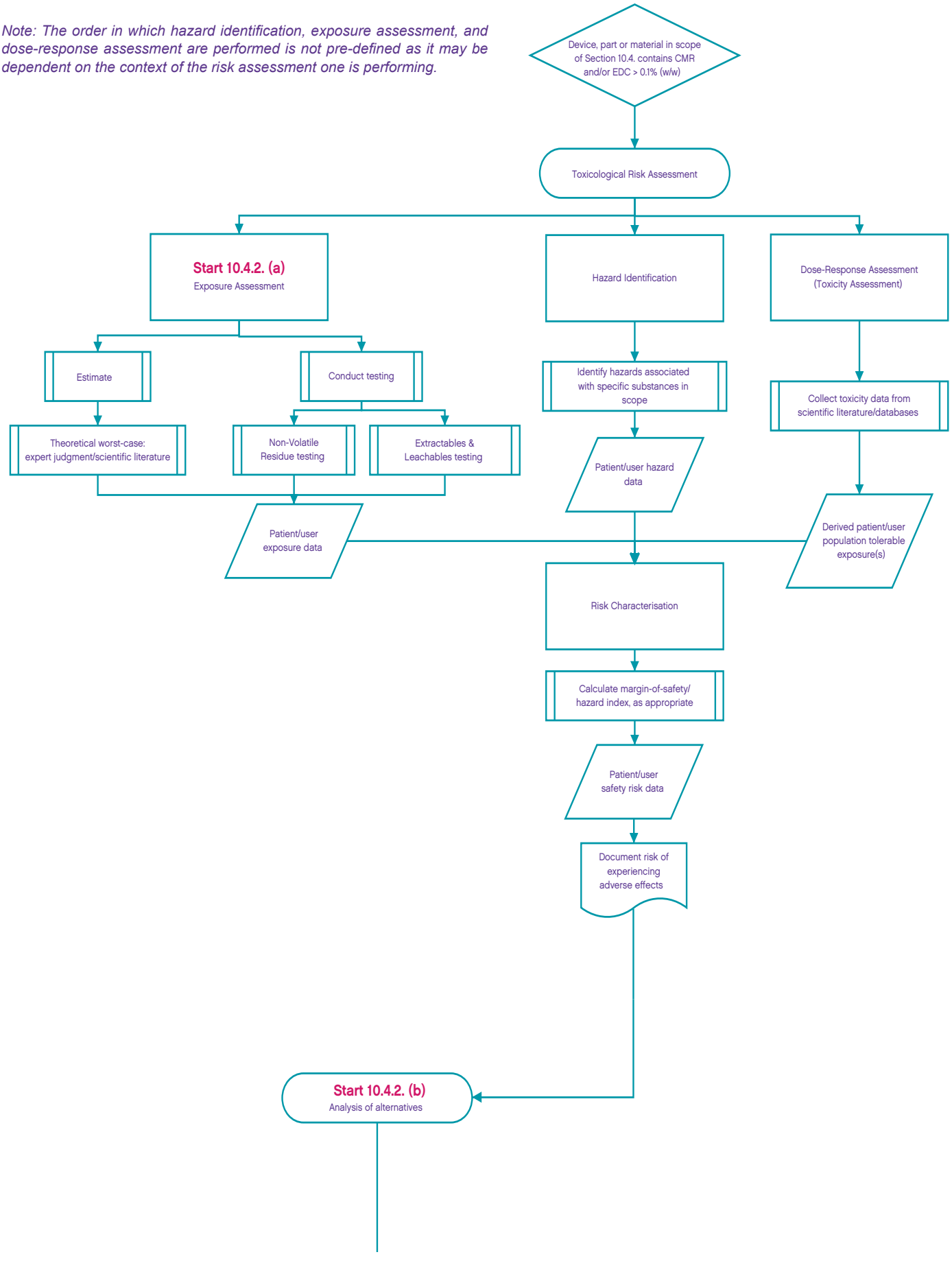
Annex I: Scope of MDR Section 10.4. (CMR 1A/1B and ED)

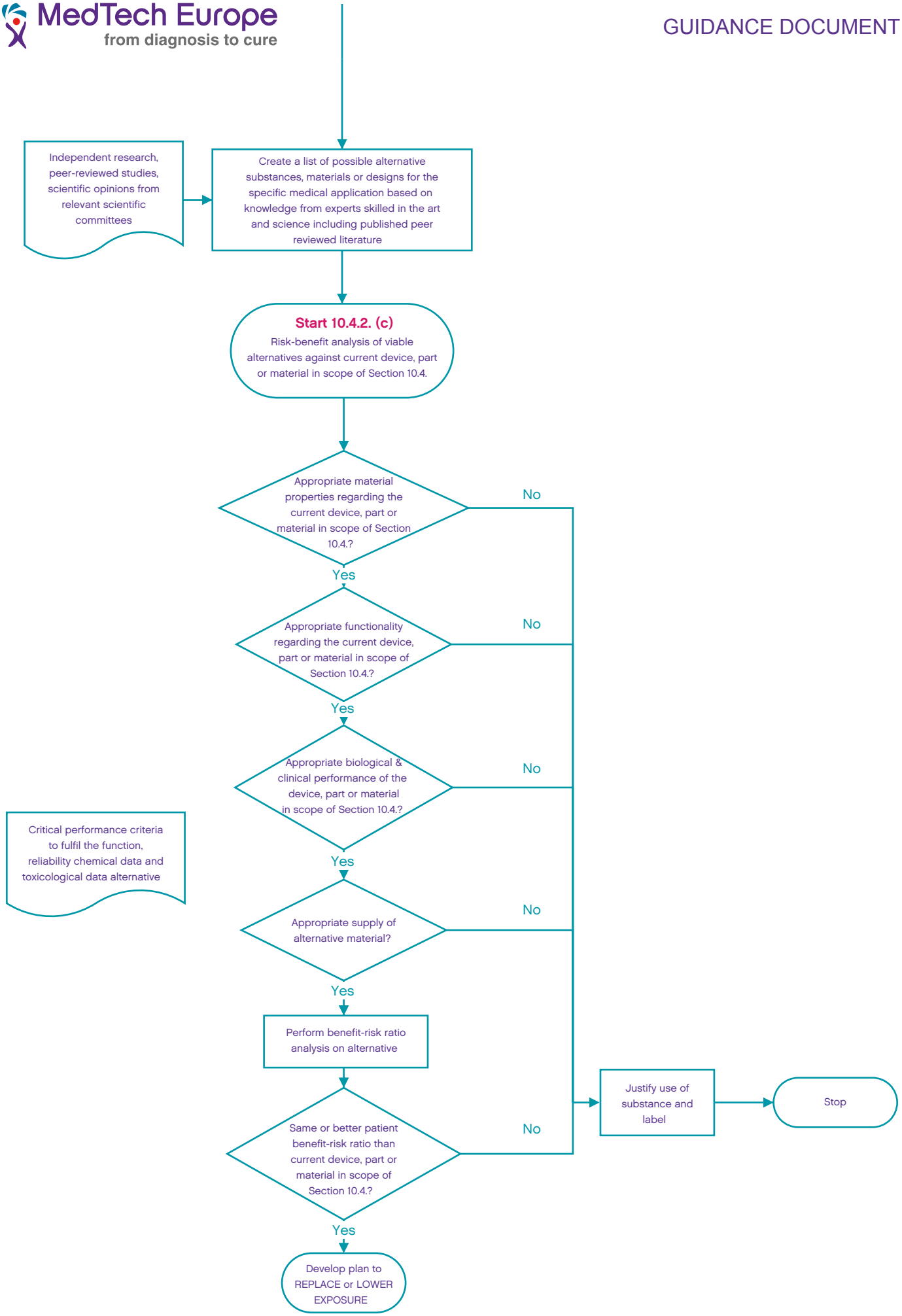


List of abbreviations:
CMR – Carcinogenic, Mutagenic, Reprotoxic chemical substances
EDC – Endocrine Disrupting Chemicals
w/w – weight by weight
AoA – Assessment of Alternatives

Annex II: Process for risk justification according to MDR Section 10.4.2.

Note: The order in which hazard identification, exposure assessment, and dose-response assessment are performed is not pre-defined as it may be dependent on the context of the risk assessment one is performing.




Independent research, peer-reviewed studies, scientific opinions from relevant scientific committees
Create a list of possible alternative substances, materials or designs for the specific medical application based on knowledge from experts skilled in the art and science including published peer reviewed literature
Start 10.4.2. (c)
Risk-benefit analysis of viable alternatives against current device, part or material in scope of Section 10.4.
Appropriate material properties regarding the current device, part or material in scope of Section 10.4.?
No
Yes
Appropriate functionality regarding the current device, part or material in scope of Section 10.4.?
No
Yes
Appropriate biological & clinical performance of the device, part or material in scope of Section 10.4.?
No
Yes
Critical performance criteria to fulfil the function, reliability chemical data and toxicological data alternative
Appropriate supply of alternative material?
No
Yes
Perform benefit-risk ratio analysis on alternative
Same or better patient benefit-risk ratio than current device, part or material in scope of Section 10.4.?
No
Yes
Justify use of substance and label
Stop
Develop plan to REPLACE or LOWER EXPOSURE

Annex III: Requirements on hazardous substances in the Medical Devices Regulation

Annex I, Chapter II

10. Chemical, physical and biological properties

10.1. Devices shall be designed and manufactured in such a way as to ensure that the characteristics and performance requirements referred to in Chapter I are fulfilled. Particular attention shall be paid to:

(a) the choice of materials and substances used, particularly as regards toxicity and, where relevant, flammability;

(b) the compatibility between the materials and substances used and biological tissues, cells and body fluids, taking account of the intended purpose of the device and, where relevant, absorption, distribution, metabolism and excretion;

[…]

10.2. Devices shall be designed, manufactured and packaged in such a way as to minimise the risk posed by contaminants and residues to patients, taking account of the intended purpose of the device, and to the persons involved in the transport, storage and use of the devices. Particular attention shall be paid to tissues exposed to those contaminants and residues and to the duration and frequency of exposure.

10.3. Devices shall be designed and manufactured in such a way that they can be used safely with the materials and substances, including gases, with which they enter into contact during their intended use; if the devices are intended to administer medicinal products they shall be designed and manufactured in such a way as to be compatible with the medicinal products concerned in accordance with the provisions and restrictions governing those medicinal products and that the performance of both the medicinal products and of the devices is maintained in accordance with their respective indications and intended use.

10.4. Substances

10.4.1. Design and manufacture of devices

Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device.

Devices, or those parts thereof or those materials used therein that:

— are invasive and come into direct contact with the human body,
— (re)administer medicines, body liquids or other substances, including gases, to/from the body, or
— transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body,

shall only contain the following substances in a concentration that is above 0,1 % weight by weight (w/w) where justified pursuant to Section 10.4.2:

(a) substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council (1), or

(b) substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council (2) or, once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council (3), in accordance with the criteria that are relevant to human health amongst the criteria established therein.

10.4.2. Justification regarding the presence of CMR and/or endocrine-disrupting substances

The justification for the presence of such substances shall be based upon:

(a) an analysis and estimation of potential patient or user exposure to the substance;

(b) an analysis of possible alternative substances, materials or designs, including, where available, information about independent research, peer-reviewed studies, scientific opinions from relevant scientific committees and an analysis of the availability of such alternatives;

(c) argumentation as to why possible substance and/ or material substitutes, if available, or design changes, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product; including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/ or materials; and

(d) where applicable and available, the latest relevant scientific committee guidelines in accordance with Sections 10.4.3. and 10.4.4.

10.4.3. Guidelines on phthalates

For the purposes of Section 10.4., the Commission shall, as soon as possible and by 26 May 2018, provide the relevant scientific committee with a mandate to prepare guidelines that shall be ready before 26 May 2020. The mandate for the committee shall encompass at least a benefit-risk assessment of the presence of phthalates which belong to either of the groups of substances referred to in points (a) and (b) of Section 10.4.1. The benefit-risk assessment shall take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments. When deemed appropriate on the basis of the latest scientific evidence, but at least every five years, the guidelines shall be updated.

10.4.4. Guidelines on other CMR and endocrine-disrupting substances

Subsequently, the Commission shall mandate the relevant scientific committee to prepare guidelines as referred to in Section 10.4.3. also for other substances referred to in points (a) and (b) of Section 10.4.1., where appropriate.

10.4.5. Labelling

Where devices, parts thereof or materials used therein as referred to in Section 10.4.1. contain substances referred to in points (a) or (b) of Section 10.4.1. in a concentration above 0,1 % weight by weight (w/w), the presence of those substances shall be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging, with the list of such substances. If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures shall be given in the instructions for use.

Annex I, Chapter III

23.2. Information on the label

The label shall bear all of the following particulars:

[...]
(f) where applicable, information labelled in accordance with Section 10.4.5.;
[...]

23.4. Information in the instructions for use

The instructions for use shall contain all of the following particulars:

[…]

(s) information that allows the user and/or patient to be informed of any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. That information shall, where relevant, allow the user to brief the patient about any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. The information shall cover, where appropriate:

— […]
— precautions related to materials incorporated into the device that contain or consist of CMR substances or endocrine-disrupting substances, or that could result in sensitisation or an allergic reaction by the patient or user;
— […]