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Commentary

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*

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ABSTRACT

By the new Medical Device Regulation (MDR, EU 2017/745) the use of certain phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties, above 0.1% by weight (w/w) is only allowed after a proper justification. The SCHEER provide Guidelines on the benefit-risk assessment (BRA) of the presence of such phthalates in certain medical devices.

The Guidelines describe the methodology on how to perform a BRA for the justification of the presence of CMR/ED phthalates in medical devices and/or or parts or materials used therein at percentages above 0.1% w/w. They also describe the evaluation of possible alternatives for these phthalates used in medical devices, including alternative materials, designs or medical treatments.

Relevant stakeholders e.g. manufacturers, notified bodies and regulatory bodies, can use the guidelines. The approach of these guidelines may also be used for a BRA of other CMR/ED substances present in medical devices.

SCHEER noticed that a number of BRA methodologies are theoretically available. However, there is a considerable lack of data needed for the BRA for potential relevant alternatives to be used in medical devices. Therefore, SCHEER encourages manufacturers to generate data of high quality on such alternatives for CMR/ED phthalates in medical devices.

The European Commission's independent Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) published guidelines on the benefit-risk assessment (BRA) of the presence of phthalates in certain medical devices. More specifically, phthalates that are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties.

The Guidelines describe the methodology on how to perform a BRA for the justification of the presence of CMR 1A or 1B and/or ED phthalates (CMR/ED phthalates) in medical devices at percentages above 0.1% by weight (w/w). They also describe the evaluation of possible alternatives for these phthalates used in medical devices, including alternative materials, designs or medical treatments.

The Regulation (EU) 2017/745 on medical devices (MDR), Annex I "General Safety and Performance Requirements", Chapter II "Requirements regarding design and manufacture", Section 10.4 deals with the presence of substances that may be released from a medical

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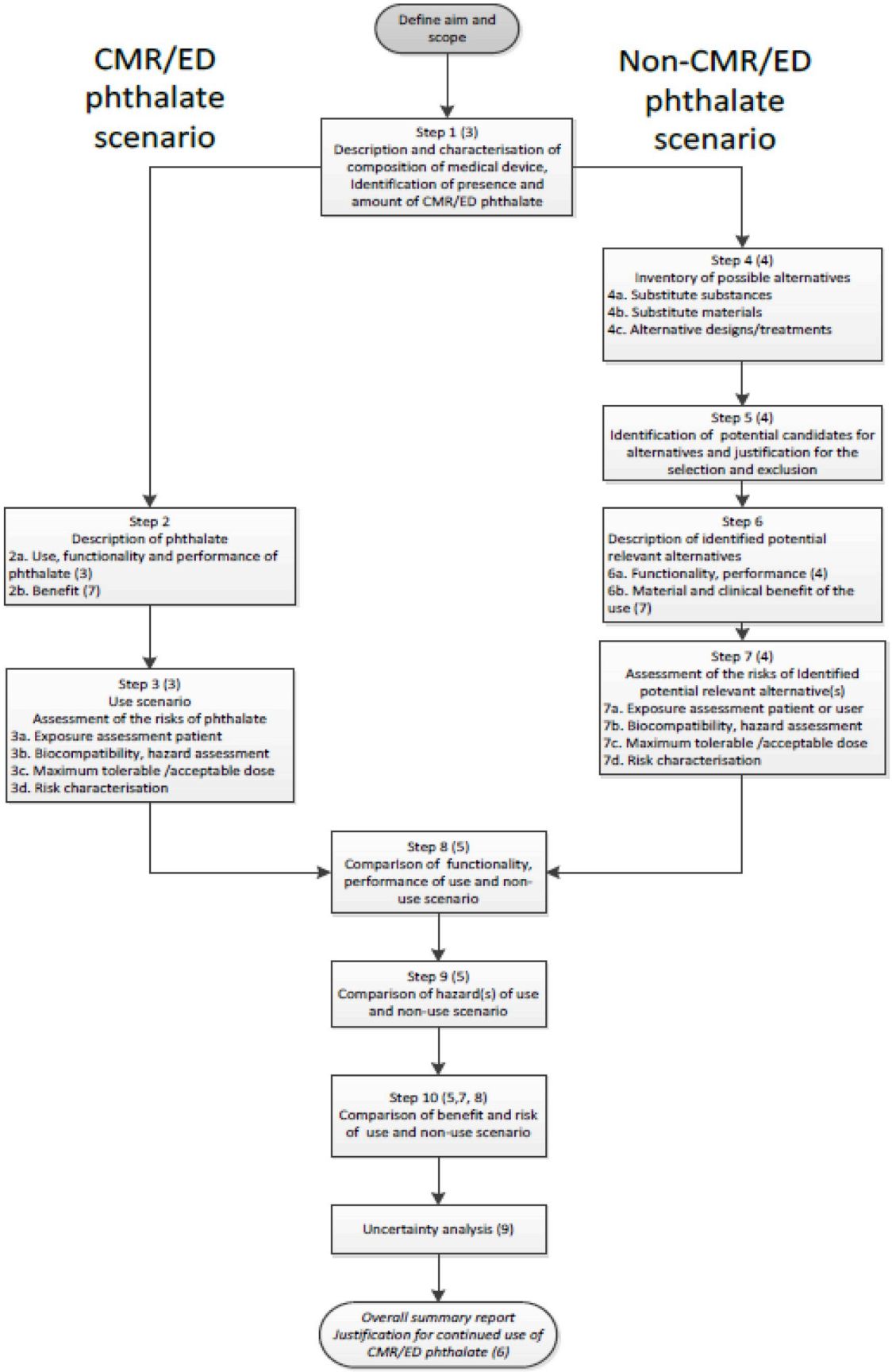

Fig. 1. BRA for evaluation of presence of CMR/ED Phthalates and their potential alternatives in medical devices (relevant sections between brackets).

device. Annex I Chapter II Section 10.4.1 states that substances that are carcinogenic, mutagenic, or reprotoxic (CMR) of category 1A and 1B, or substances having endocrine-disrupting (ED) properties for which there is scientific evidence of probable serious effects on humans, shall only be present in devices, or parts thereof or those materials used therein, above 0.1% weight by weight (w/w) when justified according to a set of criteria listed under Section 10.4.2.

These Guidelines apply to those medical devices and components thereof indicated in Annex I section 10.4.1. of the MDR. They do not provide information for the BRA of the use of a medical device itself. However, the BRA as described can be integrated within the risk management system for individual medical devices. For the BRA of medical devices in general, stakeholders are referred to section A7.2. of MEDDEV 2.7/1, revision 4. Additional information may be found elsewhere, for example in the following documents FDA 2016, 2018, EN ISO 14971, ISO/TR 24971. It should be noted that the acceptability of any risk is evaluated in relation to the benefit of the use of the medical device.

A justification for the use of a CMR/ED phthalate can also be based on an already available justification relating to a medical device for which equivalence with the device in question can be demonstrated according to the MDR Annex XIV Section 3. The existing justification can be used as a reference, and the data used for this justification should be available.

The justification for the presence of CMR 1A or 1B and/or ED phthalates for which there is scientific evidence of probable serious effects on humans should be based on a number of considerations in a stepwise approach as described below and in Fig. 1. They also provide a framework on how to assess and compare possible alternative substances, materials, designs or medical treatments to the use of CMR/ED phthalates in medical devices. An alternative could be another substance/material or device design modification or it could be a clinical procedure (e.g. a process, technique, treatment or modification) or a combination of technical and substance alternatives.

The steps:

- Assessment of the CMR/ED phthalate (CMR/ED scenario)
  - o Step 1: Description and characterisation of the composition of the medical device (or parts or materials thereof). Identification of the presence and concentration of CMR/ED phthalate(s) in weight by weight percentage.
  - o Step 2: Description of the use and function of the CMR/ED phthalate used in medical device.
  - o Step 3: Assessment of the risks of the CMR/ED phthalate.
- Assessment of possible alternative(s) (non CMR/ED phthalate scenario)
  - o Step 4: Inventory of possible alternative(s).
  - o Step 5: Identification of the potential relevant candidates for assessment as alternatives to CMR/ED phthalates and justification for the selection and exclusion of possible alternatives. This also includes assessment of the availability of the potential alternative(s).
  - o Step 6: Description of identified potential relevant alternative (s).
  - o Step 7: Assessment of the risk of identified potential relevant alternative(s).
- Assessment of potential relevant alternative(s) versus CMR/ED phthalate
  - o Step 8: Comparison of functionality and performance of CMR/ED phthalate as used in the medical device with functionality and performance of identified potential relevant alternative(s).
  - o Step 9: Comparison of hazard(s) of original CMR/ED phthalate as used in the medical device with hazard(s) of identified potential relevant alternative(s).
  - o Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified potential relevant alternatives.

This overall analysis will determine whether it is justified or not to use a CMR/ED phthalate in a medical device. The approach of these Guidelines can also be used for a BRA of other CMR/ED substances present in medical devices.

The BRA of the presence of the CMR/ED phthalate should be updated when new scientific information becomes available on alternatives for the use of phthalates, when new Guidelines are released, or as the “overall” benefit-risk determination of the medical device is updated. Pending on new scientific evidence, SCHEER recommend to evaluate the use and usefulness of these Guidelines after an application period of three years.

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None.

Reference

The guidelines in full may be read on the website of the European Commission's independent Scientific Committees, https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_015.pdf

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2019.104546.