

Guidelines on the benefit-risk assessment of the presence of phthalates in certain
medical devices



Scientific Committee on Health, Environmental and Emerging Risks

SCHEER

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



The SCHEER adopted this document at plenary meeting on 18 June 2019

ABSTRACT

The SCHEER was requested to provide Guidelines on the benefit-risk assessment (BRA) of the presence, in the medical devices specified in the regulation, of phthalates, which have one or more of the following properties: carcinogenic, mutagenic, toxic to reproduction (CMR) or endocrine-disrupting (ED), according to the criteria outlined in the legal obligation section from the mandate.

Phthalates are widely used in industry as plasticisers of polymers, in a variety of applications such as coated fabrics and roofing membranes, as well as in medical devices, adhesives, paints, inks and enteric-coated tablets. Di-(2-(ethylhexyl) phthalate (DEHP) is the most widely used phthalate in medical devices. Dimethyl phthalate (DMP) and diethyl phthalate (DEP) are not used as plasticisers but e.g. as additives in cosmetics, medical devices, and household products.

The interaction of phthalates with the polymers they are embedded in is weak, so they may be released from the plastic product into the environment and into the human body if the product is in contact with it.

The Medical Device Regulation, Regulation (EU) 2017/745 allows the use of CMR 1A/1B and/or ED substances in medical devices above a concentration of 0.1% w/w. when a proper justification can be provided (Annex I, Chapter II Section 10.4). For such a justification several steps need to be considered including the availability of alternative substances, materials, designs, and medical treatments. In addition, the risk associated with such alternatives should be weighed against the risk of the use of CMR 1A/1B and/or ED identified phthalates covered under MDR Annex I Chapter II Section 10.4.1. However, the risk by itself is not the only parameter to consider: also the impact of the possible alternatives on the functionality, performance and the overall benefit-risk ratio of the medical device shall be evaluated.

These 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 and/or or parts or materials used therein 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.

They are intended to be used by the relevant stakeholders e.g. manufacturers, notified bodies and regulatory bodies.

The approach of these Guidelines may also be used for a BRA of other CMR/ED substances present in medical devices.

During the preparation of these Guidelines for BRA of the use of CMR/ED phthalates 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.

Pending on new scientific evidence, it is recommended to evaluate the use and usefulness of these Guidelines after an application period of three years.

Keywords: Guidelines, benefit-risk assessment, CMR/ED phthalates, medical devices, SCHEER.

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ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this opinion. The members of the Working Group are:

SCHEER members:

Teresa Borges
Rodica Mariana Ion
Wim H. de Jong (Chair and Rapporteur)
Demosthenes Panagiotakos
Emanuela Testai
Theo Vermeire

SCCS members:

Ulrike Bernauer
Christophe Rousselle

External experts:

Stéphane Bégué (Etablissement Français du Sang, EFS, Paris, France)
Hilde B. M. Kopperud (Nordic Institute of Dental Materials, Oslo, Norway)
Maria Rosaria Milana (Istituto Superiore di Sanità, Dip. Ambiente e Salute, Roma, Italy)
Tanja Schmidt (Ansbach University of Applied Science, Ansbach, Germany)

Experts from EU Agencies:

Francesco Pignatti (European Medicines Agency)
Evgenia Stoyanova (European Chemicals Agency)
Katarina Volk (European Food & Safety Authority)

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SCHEER members

Roberto Bertollini, Teresa Borges, Wim de Jong, Pim de Voogt, Raquel Duarte-Davidson, Peter Hoet, Rodica Mariana Ion, Renate Kraetke, Demosthenes Panagiotakos, Ana Proykova, Theo Samaras, Marian Scott, Remy Slama, Emanuela Testai, Theo Vermeire, Marco Vighi, Sergey Zacharov

Contact

European Commission
DG Health and Food Safety
Directorate C: Public Health, Country Knowledge, Crisis management
Unit C2 – Country Knowledge and Scientific Committees
Office: HTC 03/073 L-2920 Luxembourg
SANTE-C2-SCHEER@ec.europa.eu

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A. GUIDELINES on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices

Scope

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 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 Guidelines¹ 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. They are intended to be used by the relevant stakeholders e.g. manufacturers, notified bodies and regulatory bodies.

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.

When the word “patient” is used in these Guidelines, this also covers professional users and other persons (e.g. donors in case of blood donation) exposed to the medical device as well.

Annex 1 to these Guidelines describes the mandate, Annex 2 describes Annex I Chapter II Section 10.4. of the MDR regarding the use of substances that could be released from the medical device and pose a risk to patients, and Annex 3 describes the definitions used in these Guidelines.

¹ It should be noted that, in accordance with Regulation (EC) 2017/745, Annex I, Chapter II Section 10.4.3. and 10.4.4., updates of these Guidelines might be available in the future.

1. Introduction

Placing medical devices on the market, making them available on the market and putting them into service are all activities governed by Regulation (EU) 2017/745 that replaces Directives 90/385/EEC and 93/42/EEC. Medical devices are defined in the MDR as presented in the text box below:

For the purposes of this Regulation, the following definitions apply

(1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

As a general requirement, the medical device shall perform according to its intended purpose and be safe for professional users and patients, or where applicable other persons (e.g. donors) on which the device is used. The conformity of medical devices shall be evaluated against the requirements of the Regulation (EU) 2017/745. They shall be presumed to be in conformity with this Regulation if they are in conformity with EU-harmonised standards or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union. Although not mandatory, these standards provide a route to comply with the MDR.

For medical devices the horizontal standards EN ISO 14971 and EN ISO 10993-1 are especially relevant. EN ISO 14971 describes the application of a risk management process for medical devices, whereas EN ISO 10993-1 deals with the biological evaluation and testing of medical devices within a risk management process. According to EN ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy

planned on a case-by-case basis to identify the hazards and estimate the risks of known hazards. In Annex A of EN ISO 10993-1, a series of endpoints is indicated from which a selection can be made for the biological evaluation of a medical device. The selection is based on the nature of the device's contact with the body (device category: surface device, external communicating device, or implant device; type of contact: skin, mucosal membrane, compromised surface, blood, tissues, organs; duration of the contact: limited ≤ 24 h, prolonged >24 h to 30 days, permanent >30 days). A systematic literature review is part of the biological evaluation of a medical device in order to avoid unnecessary testing (EN ISO 10993-1). This systemic literature review should also be performed for a CMR/ED phthalate or potential relevant alternatives identified for a given in a medical device.

In addition to EN ISO 10993-1, a series of EN ISO 10993 standards has been published describing various assays and approaches for the evaluation of the endpoints identified in EN ISO 10993-1 for the biological evaluation of medical devices. Assays described in the various standards include cytotoxicity, sensitisation, irritation, systemic toxicity, implantation, haemocompatibility, genotoxicity, and carcinogenicity endpoints. Additionally immunotoxicity and organ-specific toxicities need to be considered, if appropriate. In addition, reproductive and developmental toxicity should be addressed for novel materials, materials containing substances with a known reproductive or developmental toxicity, medical devices with relevant target populations (e.g. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs (EN ISO 10993-1:2018). For the risk assessment EN ISO 10993-17 describes determination of allowable limits for leachable substances, whereas EN ISO 10993-18 describes methods for chemical characterization of materials used in medical devices. In addition to the horizontal standards, vertical i.e. device specific standards and standards for clinical investigation are available (e.g. EN ISO 14155).

Furthermore, the EU also provides guidance in MEDDEV documents (e.g. MEDDEV 2.7/1 rev.4 for clinical evaluation of medical devices).

The MDR states that substances that are classified as carcinogenic, mutagenic, or toxic to reproduction (CMR) of category 1A or 1B, or substances identified at EU level as having endocrine-disrupting (ED) properties for which there is scientific evidence of probable serious effects on humans (CMR/ED substances, in this text), shall only be present in a devices or parts thereof or those materials used therein above 0.1% weight by weight (w/w) when justified. Annex 4 provides further information on the classification of CMR and on identification of ED substances. The justification for the use of CMR/ED substances in a medical device above 0.1% w/w, shall be based on an analysis of potential patient and user exposure, availability of possible alternatives, an argumentation why possible alternatives are appropriate or inappropriate, and on the most recent Guidelines of this Scientific Committee.

Phthalates are a group of substances widely used in medical devices. When used as plasticisers they may comprise a substantial part of the medical device. A typical concentration of Bis(2-ethylhexyl) phthalate (DEHP; CAS 117-81-7) in plasticised polyvinyl chloride (PVC) can be 30% based on weight (ECB 2008, SCENIHR 2015). For many years the reproductive toxicity and the possible endocrine disrupting activity of certain phthalates has been a source for debate.

Phthalates currently classified as reproductive toxicants category 1B under the Classification, Labelling and Packaging (CLP) regulation (EC 1272/2008) and identified as substances of very high concern (SVHC) under Article 57(c) of REACH Regulation (EC) 1907/2006 are listed in Annex 5 of this document. This list may be updated, so it is recommended to consult the Annex VI of the CLP Regulation.

In addition, the Commission Implementing Decision (EU) 2017/1210 and Commission Implementing Decision (EU) 2018/636 identified some phthalates as substances of very high concern (SVHC) according to Article 57(f) of REACH Regulation (EC) 1907/2006, due to their endocrine disrupting properties with probable serious effects to humans, namely Bis(2-ethylhexyl) phthalate (DEHP), Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP), Diisobutyl phthalate (DIBP), and Dicyclohexylphthalate (DCHP). Bis(2-ethylhexyl) phthalate (DEHP), was also identified in 2014 as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH. <https://echa.europa.eu/documents/10162/21837b30-0318-8b45-92db-9e8c39f89dee>

SCENIHR adopted an Opinion on the safety of medical devices containing DEHP-plasticised PVC in 2008, and a revision of this Opinion in 2015 (SCENIHR 2008, 2015). The main source for DEHP exposure of the general population was determined to be food. In addition, the use of medical devices can increase the exposure considerably in the course of specific medical treatments, for example during massive blood transfusions, haemodialysis, and in neonatal intensive care units (NICU) for prematurely born neonates (SCENIHR 2015). Although quite a number of alternative substances were available for DEHP, for some of them serious data gaps were observed regarding hazard identification and exposure estimation (Bui *et al.*, 2016, SCENIHR 2015). The Danish EPA assessed different alternatives and concluded that to various degrees some substances can be considered to be relevant alternatives to DEHP in terms of human health hazards, especially regarding the endpoints reproductive and developmental toxicity (Nielsen *et al.* 2014). However, for a number of possible alternatives the data set was limited. Some alternatives showed a low migration rate and some of them are already used as substitutes in medical devices for traditional DEHP-applications. For example, four additional plasticisers for PVC (BTHC, DEHT, DINCH, and TOTM) used in medical devices have recently been included in the updated chapters of the European Pharmacopoeia (Council of Europe, EDQM 2018).

Phthalates classified as CMR of category 1A or 1B according to the procedure described in Annex 4 are listed in Annex VI of the CLP regulation (CLP-Regulation (EC) No 1272/2008, OJ L353). According to article 57(f) of REACH (Regulation (EC) 1907/2006) or the Biocides Regulation (Regulation (EC) 528/2012) phthalates can be identified as having ED-properties when there is scientific evidence of probable serious effects to human health.

These Guidelines provide a framework of how to perform a BRA for the presence of such CMR and/or ED phthalates in medical devices or parts or materials used therein at percentages above 0.1% weight by weight (w/w), and shall be used by all relevant stakeholders, e.g. manufacturers and notified bodies, and regulatory bodies for the justification of the presence of CMR/ED phthalates. The evaluation according to the

Guidelines should be performed by a multidisciplinary team including amongst others e.g. a material scientist, medical device specialist, toxicologist and clinician.

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 approach of these Guidelines can also be used for a BRA of other CMR/ED substances present in medical devices.

Other descriptions for BRA may be "benefit-risk analysis" or "benefit-risk determination" as defined in the MDR. As Annex I Section 10.4.3 indicates a benefit-risk assessment this terminology is used in these Guidelines.

2. Framework for Benefit-Risk Assessment

The MDR allows the use of CMR 1A/1B and/or ED substances in medical devices above a concentration of 0.1% w/w when a proper justification can be provided (MDR Annex I, Chapter II Section 10.4). For such a justification several steps need to be considered including the availability of alternative substances, materials, designs, and medical treatments. In addition, the risk associated with such alternatives shall be weighed against the risk of the use of CMR 1A/1B and/or ED identified phthalates covered under MDR Annex I Chapter II Section 10.4.1. However, the risk is not the only parameter to consider. The impact of the possible alternatives on the functionality, performance and the overall benefit-risk ratio of the medical device should also be evaluated.

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 as described below and in Figure 1.

In order to perform the BRA as indicated above, it is important to describe the terminology to compare the risks of the presence of the phthalates to be evaluated (see text box below). Annex 3 provides a selection of definitions as present in the MDR and/or the OECD Substitution and Alternatives Assessment Toolbox. (<http://www.oecd-saatoolbox.org/>)

For the purpose of these Guidelines the following definition for "alternatives" is used:

<p>"alternatives are defined as substances, materials, designs and medical treatments that can be used to replace the use of CMR and/or ED substances in medical devices"</p>
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The alternative therefore is not limited to a possible substitute substance or material but could also be another device design (e.g. coating/production process/ techniques/lower concentration of substances) or medical treatment (e.g. procedure, device) or a combination of technical and substance alternatives that can substitute or eliminate the use of the CMR/ED phthalate (modified from the ECHA REACH guidance on the preparation of an application for authorisation).

The functionality and performance of the alternative should be comparable to the extent that there would be no clinically relevant difference foreseen in the performance of the

device or in the outcome of the alternative medical procedure. Considerations of functionality and performance shall be based on proper scientific justification. In order to justify the use of a CMR 1A or 1B and/or ED phthalate, the manufacturer shall clearly demonstrate that the identified alternative(s) are not appropriate to maintain the functionality, performance and benefit-risk ratios of the medical device.

A number of aspects need to be considered for the justification of the presence of a phthalate classified as CMR category 1A or 1B and/or identified as ED above content > 0.1% w/w in a medical device, or parts thereof or those materials used therein, as intended to be used.

In summary, these aspects can be considered by a stepwise approach given below and presented in Figure 1. Further details and examples on the steps used in the Guidelines are given in the following chapters.

Assessment of the CMR/ED phthalate (CMR/ED scenario)

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 (% w/w).

Step 2:

Description of the use and function of the CMR/ED phthalate used in medical device.

2a. Description of functionality/performance provided by the presence of the CMR/ED phthalate.

2b. Description of the benefit (material and/or clinical) of the presence of CMR/ED phthalate in the medical device.

Step 3:

Assessment of the risks of the CMR/ED phthalate.

3a. Determination of the patient exposure based on realistic worst-case² use scenario in the intended use.

3b. Identification of biocompatibility, general toxicological and specific CMR/ED hazards associated with the phthalate.

3c. Determination of the maximum tolerable/acceptable exposure for the patient, based on pre-clinical and clinical information (if available).

3d. Determination of the risks for various intended use scenarios and patient groups.

Assessment of possible alternative(s) (non CMR/ED phthalate scenario)

Step 4:

Inventory of possible alternative(s).

4a. Substances.

4b. Materials.

² Realistic worst case is the situation where the exposure is estimated using a range of factors (i.e. duration, amount, exposure controls), where applicable, the ones that would be expected to lead to maximum amount of exposure (e.g. exposure might be assessed under realistic simulated-use scenarios by EN ISO 10993-12 and EN ISO 10993-18 or a non-volatile residue test (USP <661>)). The realistic worst case does not include deliberate misuse. (EU Biocides Regulation 528/2012).

4c. Designs and/or medical treatments³.

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).

Step 6:

Description of identified potential relevant alternative(s).

6a. Description of functionality and performance of the potential alternative(s).

6b. Description of the benefit (material and/or clinical) of the use of the potential alternative(s).

Step 7:

Assessment of the risk of identified potential relevant alternative(s).

7a. Determination of patient exposure of the alternative based on a realistic worst-case use scenario in the intended use.

7b. Identification, where available, of biocompatibility, toxicological and CMR/ED hazards associated with the alternative.

7c. Determination of maximum tolerable/acceptable exposure of the alternative for patient (if available).

7d. Determination of risk of potential alternatives for various use scenarios and patient groups.

Assessment of potential relevant alternative(s) versus CMR/ED phthalate

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).

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).

Step 10:

Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified potential relevant alternatives.

In addition to patients, the same approach shall be used for the justification of the presence of CMR/ED phthalate in medical devices to evaluate the risk for professional users and for other persons (e.g. donors) exposed to the CMR/ED phthalates. When alternative designs or medical treatments were identified as potential alternatives in step 5, adequately adopted endpoints for risks and benefits shall be chosen.

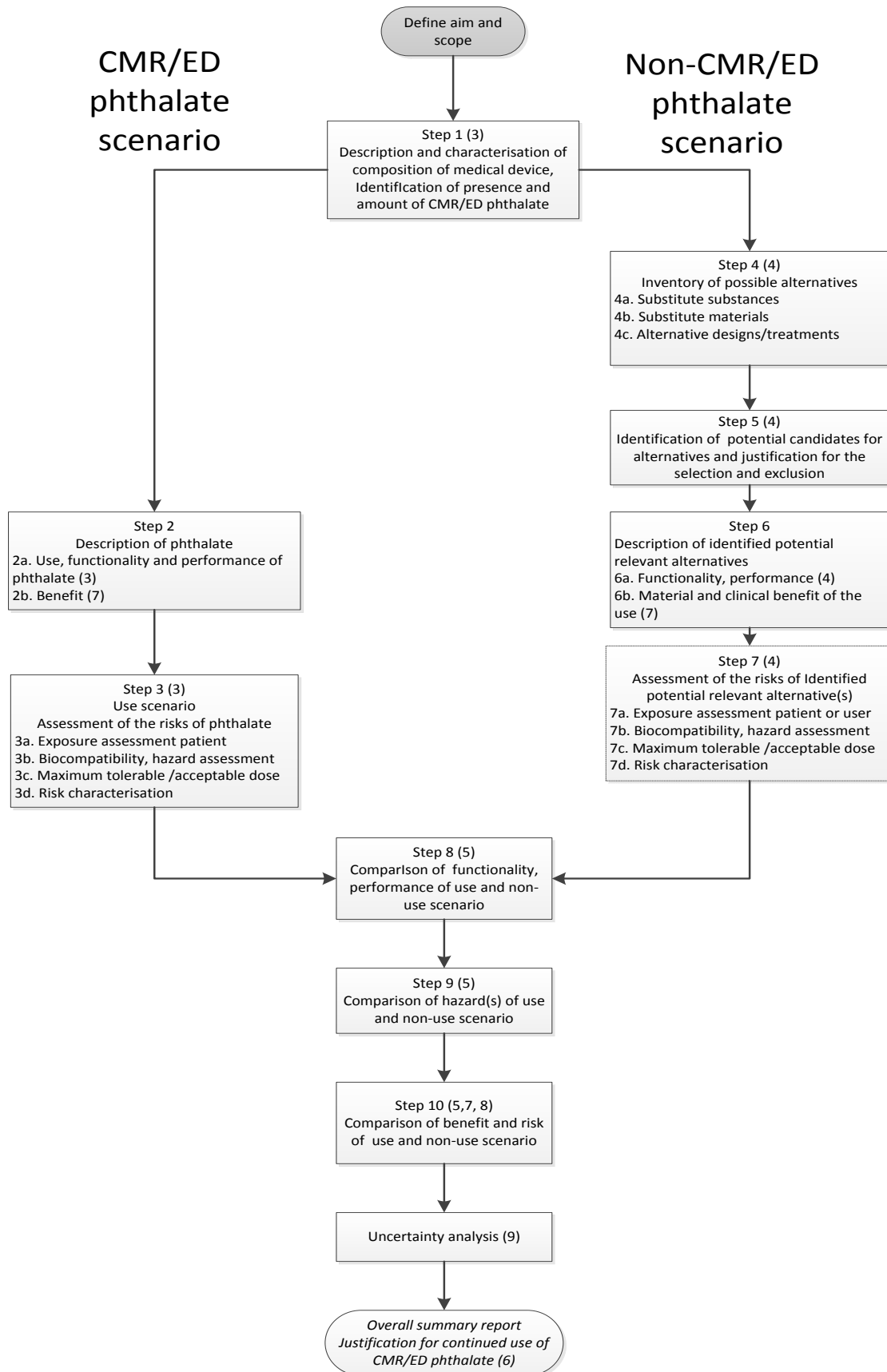
It should be noted that scientific developments may be available after the initial assessment regarding the use of alternatives for CMR/ED phthalates. Therefore, a

³ It should be noted that for alternative designs and/or medical treatments, appropriate endpoints for risks and benefits shall be selected.

revision of the BRA of the presence of the CMR and/or ED phthalate may be necessary. Revisions of the above indicated BRA shall occur as indicated in the relevant sections of MDR for the general risk assessment of the medical device.

Figure 1 illustrates the BRA and is based on Eliason and Morose (2011), EMA (2014), FDA (2016) and a critical selection from the OECD Substitution and Alternatives Assessment Toolbox (<http://www.oecdsatoolbox.org>). It presents the stepwise approach described above including a general description of factors to consider when performing a BRA. Figure 1 presents a use scenario in which the CMR/ED is used in a medical device versus a non-use scenario in which a proper potential alternative is evaluated.

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



3. Assessment of the presence of phthalates in a medical device⁴

It is already necessary to provide most of the information as indicated for the use of CMR/ED phthalates in order to prove compliance with the general safety and performance requirements for the phthalate containing medical device.

When more than one CMR/ED phthalate is used simultaneously in the medical device, a justification shall be provided for each of the phthalates and their combination. Some risk assessment data regarding the combination of phthalates are available, as EFSA has recently proposed a Group TDI for some of them, having a similar Mode of Action (MOA) *in vivo* (EFSA 2019, see Annex 5). Information on assessment of combined exposures to phthalates can be found for example at the report by the National Research Council Committee on the Health Risk of Phthalates (2008) and the ECHA website on the restriction of four phthalates (<https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180d73895>) and EFSA guidance on cumulative exposure (EFSA, 2019 <https://doi.org/10.2903/j.efsa.2019.5634>)

Step 1: Description and characterisation of the composition of the medical device.

Provide a description of the medical device and its composition including identification and the concentration of each CMR/ED phthalate in the device, and the type of chemical /physical binding of the phthalate in the formulation/device, when there is an impact on leakage. Use available chemical information for identifying target phthalates (e.g. CAS N°; EINECS N°; IUPAC name). The chemical composition of a medical device can be evaluated by using e.g. EN ISO 10993-18 (FDIS published in 2019).

Step 2: Use and function of CMR/ED phthalates in the medical device.

Characterise the function and use of the CMR/ED phthalates in the medical device and the properties it imparts to the device. Provide a description of the intended use, functionality and performance of the medical device containing the CMR/ED phthalate and how the use of the phthalate is critical for its functionality and performance. For example, for PVC consider, with regard to the performance of the medical device, maintenance, flexibility, durability and for the phthalate viscosity and PVC compatibility. Provide a description of the patients targeted (e.g. with respect to sex, age, probable vulnerable groups⁵). Provide a description of use types of the medical device for which it is intended (e.g. single vs repeated exposure). Other aspects that can be relevant include the critical properties (e.g., flexibility), the conditions of use, critical quality criteria, process/treatment and performance constraints (e.g., sterilization, device/drug interactions), regulatory or clinical or other requirements that the CMR/ED phthalates and the phthalate-containing device need to deliver. Key criteria for the function,

⁴ The analysis presented in section 3 (steps 1-3) describes the current use scenario of the CMR/ED phthalate, i.e., the scenario that would continue in the future if no additional action (other than, e.g., a planned regulatory action entering into force) is taken to limit, substitute or eliminate the presence of the CMR/ED phthalate in the medical device. The current scenario can also be referred to as baseline, business as usual or continued use scenario.

⁵ Vulnerable Groups (in these Guidelines): vulnerable groups of the population such as children and individuals with increased susceptibility due to pre-existing disease, medication, compromised immunity, pregnancy or breastfeeding, women and men in reproductive age. These vulnerable groups also include infants, elderly people or people with poor health conditions.

performance and overall use should be outlined and applied as the basis for an identification and screening of possible alternatives and a more detailed assessment of potential alternatives. Justification for the selection of these criteria should be provided.

Benefits of the device with CMR/ED phthalates should also be considered e.g. treatment of specific patients groups due to tuning of flexibility of the medical device. Present an inventory of the benefits of the CMR/ED phthalates in the medical device for the patients (separately for vulnerable groups). More detailed information on the benefit assessment is presented in section 7.

Step 3: Assessment of the risks of the CMR/ED phthalate.

Perform a risk assessment of the CMR/ED phthalate present in the medical device. The risk assessment should contain a description of the potential phthalate exposure of various patient groups for which the medical device is intended (e.g. single vs repeated exposure). This should separately include vulnerable groups. EN ISO 10993-1 provides information on use type in terms of exposure potential (e.g. limited (≤ 24 h), prolonged (>24 h to 30d) and permanent (>30 d)) that slightly differs from the duration of use as defined in the MDR (Annex VIII, 1, transient <60 minutes, short term 60 minutes to 30 days, long term >30 days).

Exposure estimation

Provide information, preferably based on data from direct measurement or, when not available, an estimation based on worst-case scenario or from scientific literature, on the release of the CMR/ED phthalate from the medical device when used in various clinical modalities. For data generation, analytical contact conditions for the evaluation of leaching of substances from medical devices, should consider for example temperature, contact duration and frequency, polarity of contact liquids, flow rates, contact surface, and volume of contact liquids (EN ISO 10993-1, EN ISO 10993-12, EN ISO 10993-18, USP 661). The contact conditions should be set to represent realistic worst-case conditions taking into account the intended use of the medical device.

Estimate exposure to the phthalate(s) considering data on the release of the substance from the device. Consider repeated use scenarios (e.g. dialysis, apheresis donation, chronic treatment) and different population groups. The combined exposure to different CMR/ED phthalates also needs to be considered when present in a medical device. More details on the use of phthalates in medical devices are presented in Annex 6. Risk management measures in place and their effectiveness should be described and taken into account in the assessment (EN ISO 14971, EN ISO 10993-1). In addition, data from biomonitoring programs may become available that could also provide information on exposure levels of phthalates in the general population and more specifically during medical treatment.

Hazard identification

Describe hazards associated with the CMR/ED phthalate by considering all relevant toxicological endpoints for acute as well as for repeated dose toxicity. EN ISO 10993-1 provides information on hazard endpoints to be considered depending on the exposure and use category of a medical device, whereas allowable limits can be determined according to EN ISO 10993-17. Possible hazardous effects of combined exposure should

also be assessed. Identify an adequate point of departure (PoD) for risk assessment. In case of a threshold Mode of Action, such a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD) obtained by Benchmark dose modelling. In case of non-threshold effects (e.g. in the case of genotoxic carcinogens or for certain substances acting via an ED-mediated MoA), such a dose descriptor could be a T25⁶ value or the benchmark dose associated with a 10% response (BMD10) (ECHA, 2012).

Where a reference DNEL and/or a reference DMEL have already been derived in the context of other EU legislations, the analysis could refer to these derived figures without referring to detailed assessment how these data have been derived (e.g. under REACH legislation, Food Contact Material legislation). However, as some of these data may have been derived in the past, relevant up-to-date scientific evidence (based upon a systematic literature review) and up-to-date risk assessment methodology for all relevant toxicological endpoints needs to be considered. If such DNEL/DMELs are not used in the assessment, a justification should be presented (e.g. new information/studies). Some of these other legislations are defined under Annex 4. In addition, information can also be obtained in the SCENIHR 2015 Opinion on DEHP.

The ED property of the phthalate can be described according to the recently published EFSA/ECHA guidance document.

<https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>

This includes impacts on fertility, birth defects (e.g., cryptorchidism, hypospadias), developmental effects, and other effects associated with the CMR/ED phthalates.

Describe risk (risk characterisation)

The risk can be described by comparing exposure levels that are considered safe with the expected exposure (worst-case scenario) to obtain a risk characterisation ratio (RCR). Starting points (points of departure, PoD) for exposure levels that are considered safe could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD) for threshold substances. For non-threshold substances, a T25 value or the benchmark dose associated with a 10% response (BMD10) could be used. From these PoDs, acceptable exposure values can be derived such as “Derived No-Effect Level” (DNEL), “Derived Minimum Effect Level” (DMEL) or intakes over lifetime without presenting an appreciable risk to health (ADI or TDI/TWI or TE). As such data are often obtained in rat studies, the use of the TDI seems more appropriate in view of the critical effect window for androgenic reproductive toxicity in rats has been reported to be a few days (Welsh *et al.*, 2008). In addition, patients may be exposed to medical devices only for a limited period of time. EN ISO 10993-17:20027 calculates for medical devices a Tolerable Exposure (TE), which is based on a product of the tolerable intake, the body mass and the utilization factor. When necessary, acceptable exposure levels can be derived by dividing the point of departure for risk assessment by appropriate assessment or uncertainty factors. Specifically for ED effects additional assessment factors might be considered as proposed recently (Hass *et al.*, 2019).

⁶ Animal dose-descriptor; chronic dose rate that will give 25% of the animal's tumours at a specific tissue site after correction for spontaneous incidence (Dybing *et al.*, 1997)

⁷ EN ISO 10993-17:2002 is currently under revision. It is discussed to replace in the updated version TE by TI.

The risks can also be described by calculation of the Margin of Safety (MoS), which is the ratio between the lowest PoD and the expected exposure (worst case scenario) and comparison with a reference MoS (see SCCS Notes of Guidance – SCCS/1602/18). Perform this evaluation for every group (patients/donors) for which the device is intended to be used.

Determine and describe in which situation the risk can be acceptable for the use of the CMR/ED phthalate in the medical device. The benefit-risk assessment for the use of the CMR/ED phthalate can be performed using for example MEDDEV 2.7/1rev4 and EN ISO 14971 (see also Section 8). The MDR considers a risk acceptable when outweighed by the benefit of using the device in patients (Chapter I of MDR, Chapter VI Article 62).

In addition to potential CMR/ED effects, discuss any other potential hazards associated with the composition of the device (e.g. by using the EN ISO 10993 series of standards). Evaluate if such effects are associated with the use of the CMR/ED phthalates in the device.

Note: It should be noted that for some genotoxic carcinogens a no effect level is assumed not to exist. Similarly, a scientific debate is ongoing about whether this also applies to ED activity.

The assessment of the risk should be accompanied by an estimation of the impact of uncertainties in the described outcomes (see section 9).

4. Assessment of possible alternative substances, materials, designs or medical treatments⁸

In general a similar risk assessment as presented in step 3 above has to be performed for the alternative (substances, materials, designs or medical treatment). An inventory should be prepared in order to be able to evaluate possible alternatives. 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.

Step 4: Inventory of possible alternatives

Prepare a list of possible alternatives (such as substances, materials, designs or medical treatments)⁹.

A description of the alternative scenario (CMR/ED phthalate "non-use scenario") needs to be presented including identification of alternative substances, materials, designs or medical treatment, e.g. by including consideration of all available information, such as alternative medical devices available on the market, information about independent research, published peer-reviewed studies, systematic literature reviews, risk assessment reports or scientific opinions from relevant scientific committees and the results of in-

⁸ The analysis presented in section 4 constitutes the non-use scenario or the scenario that would transpire if the CMR/ED phthalates would no longer be used in the medical device.

⁹ Information source for alternatives might be the European Pharmacopoeia.

house research and development. The identification of possible alternatives should be properly documented.

Step 5: Identification of the candidates for assessment as potential relevant alternatives for phthalates

The MDR indicates that an analysis of all possible alternatives shall be performed. However, when many alternatives are available it would not be feasible to do an extensive evaluation of all alternatives. It is therefore recommended to select a number of potential relevant alternatives based on screening against key criteria for function, performance, toxicity, and overall use in the medical device in question (see below). In addition, analysis of availability and technical feasibility might affect choices for alternatives as well.

A preliminary analysis of possible alternative substances, materials or designs or medical treatments should be performed. This preliminary analysis should include a description of their possible use as alternative substance, material, designs or medical treatments. Justification on how and why alternatives are rejected for further assessment by defining inclusion and exclusion criteria should be provided.

Information/data on functionality (e.g. level of flexibility in tubes) as well as performance and/or chemical safety assessment (e.g. hazard profile) may be used for rejection of the less likely alternatives (see below) and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The chemical safety assessment should be done after assessment of the functionality and performance.

In addition to the comparison in terms of functionality, technical performance and risks to patients and users, which are critical elements for the benefit-risk assessment, Annex I Section 10.4.2 of the MDR states that the justification for the presence of CMR/ED substances should also be based on an analysis of the availability of possible alternatives. Availability has several aspects, including for example the availability of necessary quantity (volumes) of the alternative on the market within a required timeframe and the ability to gain access to alternatives that may be proprietary (e.g., via licensing).

If potential alternatives can be identified, a shortlist of the potential alternatives can be established for further detailed assessment with regard to technical feasibility, health benefits, comparison of risks, existing legal requirements, availability (e.g. sufficient availability or accessible to the manufacturer), and technical performance. In the event that no alternative is identified, information should be presented on the actions undertaken to identify alternatives.

A compilation of resources and elements in support of chemical substitution and an assessment of alternatives can be found on the OECD webpage:

<http://www.oecdsatoolbox.org/>

Step 6: Description of identified potential relevant alternative(s) and conclusion on their technical feasibility

CMR/ED phthalates are present in medical devices for a specific purpose depending on the intended use of the medical device. For example, phthalates offer the possibility for fine tuning the flexibility (e.g. optimal flexibility without kinking) of a PVC-based medical

device. In addition, DEHP has a stabilising effect on red blood cells in blood bags (SCENIHR 2015). Technical feasibility of an alternative is based on the alternative fulfilling the function of the CMR/ED phthalate. Therefore, the assessment of the functional properties in relation to the intended use of the medical device is essential. Besides functionality, performance under intended use conditions should also be considered.

Argumentation shall be provided for justifying why possible substances and/or material substitutes, if available, or design or medical treatment changes, if feasible, are inappropriate in relation to maintaining the functionality and/or performance of the medical device. For example, it might be the case that replacement is possible for one specific functional use whereas for another functionality the use of the CMR/ED phthalate remains necessary. Also other aspects related to performance of the alternatives need to be considered like material processing conditions (Crespo *et al.*, 2007), material quality after sterilisation (Burgos and Jiménez 2009), and possible interaction with drugs in therapeutic infusion systems (Treleano *et al.*, 2009, Salloum *et al.*, 2015, Tortolano *et al.*, 2018).

The benefit(s) should also be considered. An inventory of the benefit(s) of the potential alternative substances, materials, designs or medical treatments for patient populations (separately for vulnerable patient groups) should be presented (see section 7).

The evaluation of the identified potential relevant alternatives can be done in a tiered way to avoid full assessments for each candidate alternative. For example, based on the outcome of the functionality evaluation, the choice of the potential relevant candidates might be reconsidered and some might be discarded before performing the risk assessment (see Step 7).

The ECHA guidance on the preparation of an application for authorisation and ECHA formats for Analysis of Alternatives provide more detailed information on how to conduct an initial screening of possible alternatives and to assess the technical feasibility of potential alternatives. Submitted applications for authorisations contain a number of examples (<https://echa.europa.eu/applying-for-authorisation/preparing-applications-for-authorisation>) of technical feasibility assessment for uses of substances of very high concern.

Step 7: Assessment of the risk of identified potential relevant alternatives

The risk assessment of alternatives is comparative in nature. Its aim is to assist in the conclusion in section 5 whether the transition to the alternatives would lead to lower benefit and/or risk to human health for patients when compared to the current use of the CMR/ED phthalates in the medical device. The methodology of the assessment in this step is similar to that in step 3 as performed for the phthalate to be evaluated with reference to the alternative.

If potential relevant alternatives were identified under Steps 1-6, a risk assessment of these potential relevant alternative substance/material or designs or medical treatments should be performed. The risk assessment should contain a description of the potential substance/material (alternative medical procedure) exposure of various person groups (e.g. including patients, donors, professional users) for which the medical device is intended to be used (considering single or repeated use). This should include separately

vulnerable groups. For each subgroup a different level of risk may be accepted based on the potential benefit of the medical device for that particular group. Risk management measures (EN ISO 14971, EN ISO 10993-1) and their effectiveness to reduce exposure should be described and taken into account in the assessment.

Exposure estimation

Estimate the potential release of the alternative substance(s) when used in various treatment modalities. Consider also the rate of leaching to estimate the potential exposure to the alternative substance. Multiple use scenarios (including various types of possible contact) should be considered for the exposure estimation of the alternative substance (e.g. frequent use of dialyzer) and different population groups.

Hazard identification

Identify hazards based on literature, supplier documentation and other information (such as risk assessments performed by regulatory bodies). Describe hazards associated with the alternative substance/material by considering all relevant toxicological endpoints for acute as well as for repeated dose toxicity including human data. Identify an adequate point of departure (PoD) for risk assessment. In case of a threshold Mode of Action, such a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD) obtained by Benchmark dose modelling. In case of non-threshold effects (e.g. in the case of genotoxic carcinogens or for substances acting via an ED-mediated MoA), such a dose descriptor could be a T25 value or the benchmark dose associated with a 10% response (BMD10) (ECHA, 2012). Hazards should preferably be evaluated by a relevant exposure route for the intended use of the assessed medical device.

For the hazard identification special attention should be on the determination of any potential CMR and/or ED property of the alternative substance used. For further information purposes, a procedure is described in ECHA Guidance on the application of the CLP criteria

https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5

or by searching Annex VI of CLP regulation. ED properties of the alternative substance/material can be described according to the recently published EFSA/ECHA guidance document.

https://echa.europa.eu/documents/10162/23036412/bpr_guidance_identif_ed_en.pdf/1a4d2811-3faa-fe61-1de2-3cbce8fd4d95

These effects include impacts on fertility, birth defects (e.g., cryptorchidism, hypospadias), developmental effects, and other potential toxic effects associated with phthalates with ED properties and reprotoxic effects category 1A/B. It needs also to be considered that the potential alternative (substances, materials, designs or medical treatments) could also have other hazards than those of the CMR/ED activity. These other hazards and their possible associated risks should be discussed for example by using the EN ISO 14971 and the EN ISO 10993 series. See also Table 1.

Description of risk (risk characterisation)

The risk can be described by comparing exposure levels that are considered safe with the expected exposure (realistic worst case use scenario). Exposure levels that are considered safe could be "Derived No Effect-Levels" (DNELs) for threshold substances, "Derived Minimum Effect Levels" (DMELs) for non-threshold substances or intakes over lifetime without presenting an appreciable risk to health (ADI or TDI/TWI or TE). As such data are often obtained in rat studies, the use of the TDI seems more appropriate in view of the critical effect window for androgenic reproductive toxicity in rats has been reported to be a few days (Welsh *et al.*, 2008). In addition, patients may be exposed to medical devices only for a limited period of time. EN ISO 10993-17:2002 calculates for medical devices a Tolerable Exposure (TE), which is based on a product of the tolerable intake, the body mass and the utilization factor. When necessary, acceptable exposure levels can be derived by dividing the point of departure for risk assessment by appropriate assessment or uncertainty factors. For medical devices allowable limits of their chemical constituents can be determined by EN ISO 10993-17.

The risks can also be described by calculation of the Margin of Exposure (MoE) or the Margin of Safety (MoS) due to the substances present in a medical device, which is the ratio between the lowest PoD and the expected exposure (e.g. realistic worst case use scenario) and comparison with a reference MoS (see SCCS Notes of Guidance – SCCS/1602/18).

Perform this evaluation for every patient group for which the device is intended to be used.

Where a reference DNEL and/or a reference DMEL have already been derived in the context of other EU legislations, the assessment could refer to these derived figures without referring to a detailed assessment of how these data have been derived (e.g. under REACH legislation, Food Contact Material legislation). Data on the relevant exposure route of the medical device application (e.g. intravenously) are preferred (see also Table 1A, EN ISO 10993-1). The risk can be described by the so-called risk characterisation ratio (RCR), being a ratio between the exposure and the DNEL/DMEL. If such DNEL/DMELs are not used in the assessment, a justification should be stated (e.g. new information/studies).

Determine and describe acceptability of the risk for the use of the potential alternatives. Risks may be acceptable when they are outweighed by the benefits for the patient.

Consider any known adverse events associated with the operation of the device using the phthalate, and whether the potential alternatives might affect these adverse events. These considerations can be based upon a systematic literature review (see MEDDEV 2.7/1rev4).

This exercise has to be performed for each potential relevant alternative substance and/or materials.

A large number of phthalates exist and some may be potential relevant alternatives for the CMR/ED phthalate used in the medical device. However, a number of these phthalates are also classified as CMR and/or designated ED (see above and Table 1 Annex 5). Such phthalates might be identified as alternatives when the CMR/ED risk is reduced compared to the phthalate intended to be used. In addition, different substances, have also been proposed as alternative plasticisers. In 2015 SCENIHR published an updated Opinion of potential alternative plasticisers for DEHP (SCENIHR

2015). Although many alternatives were potentially available, it was also observed that for many of them the information on potential risks and the necessary risk assessment was rather limited precluding their use as alternatives. For DEHP an extensive amount of literature is available, allowing a very careful evaluation of the risk associated to its use.

In the event that the risk assessment of a potential relevant alternative cannot be performed due to lack of information, documentation should be presented on the actions undertaken to obtain information to characterise the risk, including the outcome (for example, QSAR /read across could be performed).

Note shall be taken that alternative designs or medical treatments might lead to adaptation of endpoints for the benefit-risk assessment when compared to the toxicological endpoints of CMR/ED phthalates.

The assessment of the risk should be accompanied by an estimation of the uncertainties in the described outcomes which might be quantitative (e.g. confidence interval, standard deviation) or qualitative (see section 9).

Conclude the analysis of the potential relevant alternative(s) with a summary describing the possible scenario(s) (see Figure 1).

5. Assessment of potential relevant alternative substances, materials, designs or medical treatments versus CMR/ED phthalates

Based on the information obtained above a decision can be made on the appropriateness of potential relevant alternatives (substance, material, design or medical treatment). In this evaluation several factors need to be included such as weighing of technical feasibility, benefits and risks. And, if possible, quantification of benefits and risks. These steps entail a comparison of the CMR/ED phthalate "use-scenario" (summarised in step 3) with the "Non-use scenario" (summarised in step 4) as shown in Figure 1.

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).

Compare the functionality and performance of CMR/ED phthalate in the medical device and the potential relevant alternative substance/material (or designs or medical treatments by choosing adequate endpoints).

Perform step 8 for each candidate identified as the potential relevant alternative in section 4.

If several potential relevant alternatives have a similar functionality and hazard profile, exposure conditions and possibilities for Risk Management Measures (RMM) resulting in risk reduction should be considered (see below). Risk management is described in EN ISO 14971.

In this comparison also additional issues not directly related to the functionality and performance of the alternative itself, like technical possibilities, sterilisation effects and

interactions with infusion liquids, are important for the application of the alternative and the comparison with the CMR/ED phthalates, and thus should be considered.

Step 9: Comparison of risk(s) of CMR/ED phthalate as used in the medical device with risk(s) of identified potential relevant alternatives.

Compare the risk of both CMR/ED phthalate and alternative substance/material (or designs or medical treatments by choosing adequate endpoints).
Perform step 9 for each potential relevant alternative.

There may be difficulties in comparing the risks of a substance e.g. a phthalate, and the risks of a technical alternative such as medical design or medical treatment. For example, there may be risks associated with alternative technologies but these may not be of the same nature of the risk of the phthalate. However, the potential relevant alternative must represent a reduction in the overall risks to human health (Step 10). Therefore, a comparison of risks must be conducted and the applicant will need to consider how these different risks might be compared in terms of risks to human health. Note that an alternative medical design or medical treatment may also result in exposure to other risks previously not present in the treatment modality. Possible risks of these substances will also need to be considered in the assessment. The comparison with technological alternatives such as a medical design or medical treatment can normally not be fully quantitative (i.e. with directly comparable numeric values), as the hazards and associated risks will not be expressed in similar terms, but will in most cases be qualitative or semi-quantitative. Nevertheless, a clear and transparent description can give a good basis to conclude whether overall risks are reduced or not (Step 10).

Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified potential relevant alternatives.

Present summary/overview of comparison of benefit and risk of CMR/ED phthalate used in the medical device with the potential relevant alternatives, including uncertainties about the estimates or reliability of the data, assumptions, etc. for the parameters presented. The summary should contain various aspects of functionality, performance, risk and benefit of the use of the original CMR/ED phthalate used in the medical device and the potential relevant alternative(s). In section 6 below the justification of the use of a CMR/ED phthalate is described based on the summary table comparing an alternative with the CMR/ED phthalate.

Perform step 10 for every potential relevant alternative.

Each of the assessments performed in steps 1 to 10 is associated with uncertainties. Certain uncertainties can be described by the use of measures like the standard deviation or confidence interval. For other uncertainties, a description may be necessary to explain the extent of the uncertainty and its impact on the final outcome.

Benefit and risks should be described and weighted against each other in the use of the potential alternative substance/material in the medical device (or designs or medical treatments by choosing adequate endpoints) similar to the procedure for the CMR/ED phthalate (see step 2).

6. Justification for the use of CMR/ED phthalate

Based on the comparison of functionality, performance, availability, risk and benefit, an argumentation can be built as to why a possible substance and/or material alternative, if available, or changes in designs or medical treatment, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratio or profile (quantitative/semi-quantitative or qualitative) of the medical device containing a CMR/ED phthalate.

Explain the importance of any difference in terms of benefits and risks between the CMR/ED phthalate to be used in the medical device and potential relevant alternatives using value judgements and explain how the use of the CMR/ED phthalate can be justified over the alternatives by describing the acceptability of trade-offs in the achievement of some criteria against others. Any advantage in benefits needs to be weighed against possible disadvantages in terms of functionality and risks. Both differences in benefits and risks need to be considered jointly.

In building the argumentation for the use of a CMR/ED phthalate, note can be taken of the Memorandum on weight of evidence and uncertainties of SCHEER (SCHEER 2018). This Memorandum describes a methodology that classifies the strength of evidence in the human health risk assessment based on integration of different lines of evidence into strong, moderate, weak, uncertain and inconclusive (no suitable evidence available). Any weight of evidence evaluation needs to show the overall confidence in the assessment.

The argumentation should specifically take into account the intended use of such devices. This should include consideration and discussion of possible high risk groups such as children or pregnant or breastfeeding women, and other patient groups considered particularly vulnerable to such substances and/or materials. In addition, where applicable and available, any future update of these Guidelines shall be considered. A Table with the most relevant information and values should be used to present an overview of the performed assessment comparing the CMR/ED phthalate with potential alternative(s). A non-exhaustive example of such Table is presented below. The Table should be extended depending on the number of criteria evaluated and the number of potential alternatives identified.

Table 1: Example for a comparison of CMR/ED phthalate with potential relevant alternative(s).

Assessment criteria	Description (examples)	Reference phthalate	Alternative I	Alternative II etc.
Identification of substances/material etc Name and CAS number	Chemical information	CAS 117-81-7		
Functionality/performance	Used as plasticiser	e.g. DEHP		
Clinical benefit/performance	Treatment possibility	e.g. Flexibility of tubing / red blood		

		cells storage		
Material benefit				
Concentration (% w/w)				
Leaching from medical device for relevant conditions e.g. media, temperature, etc (mg per hour/day)				
Exposure estimation (realistic worst case use scenario) for relevant route of exposure				
Hazard identification	Local and systemic acute and repeat-dose toxicity, ED-properties, organ toxicity, CMR properties, biocompatibility, and others			
Identification of a point of departure for risk assessment (LOAEL, NOAEL, BMD, T25, BMD10)				
Identification of dose levels associated with minimal or negligible risk (e.g. DNEL, DMEL, TDI, TE, TI)				
Risk characterisation (MoE, MoS, RCR)				
Confidence estimation (see Table 2)				
Technical feasibility				
Other				

This Table shall be completed for every component of the medical device that contains CMR/ED phthalate(s) above the 0.1% w/w level. For some medical devices used as a system (e.g. blood bag system) the whole system might be evaluated. Note that in case of alternative designs or medical treatments adequate endpoints for the comparison shall be chosen. These endpoints may represent risks that may be of a different nature than that of the risk of the phthalate.

When the outcome of the comparison shows that the alternative fulfils a comparable or better intended functionality as well as performance and shows a reduced risk, the use of a CMR/ED phthalate is not possible. The risk assessment should also indicate whether there would be a reduced hazard concerning CMR and/or ED properties, and/or reduced exposure overall resulting in reduced risk. In this evaluation, other toxicities (e.g. for any

other organ or system) of the potential relevant alternatives shall also be considered. So, the full toxicological profile of the potential relevant alternatives shall be taken into account.

A balanced weighing of the benefit versus the risk has to be performed. For example it is possible to use a combination of a CMR/ED phthalate and PVC/material with high intrinsic toxicological hazards, thus accepting a risk from a toxicological perspective, in case the clinical benefit is very high. In contrast, a minor loss in medical functionality might be acceptable if there is a large reduction or even absence of risk. Each comparison of a potential alternative for the use of a phthalate should be based on the combination of functionality, risk and benefits for patients.

In this final evaluation, the assessment of uncertainties associated with the alternatives (e.g. on the nature of the risks; assumptions made) should also be considered (see Table 2 below section 9). Therefore, where possible, quantitative results should be collected and compared (e.g. NOAEL, estimated exposure in mg/kg) and their uncertainties should be reported. Also a qualitative description of the uncertainties may be useful (see Table 2 below section 9). Their impact on the conclusions should also be discussed.

Although not the main subject of these Guidelines, it should be realised that availability and accessibility on the market might be a limitation for the introduction of an alternative substance/material. Some chemicals proposed as alternatives are widely available (e.g. BTHC, DEHT, DINCH, and TOTM) however, this may not be the case for other alternatives identified. The lack of the availability of a potential alternative for a medical device might result in the conclusion that replacement is not feasible and that the use of a phthalate with CMR and/or ED property continues in order to keep the device available for patients. So, besides technical feasibility in terms of functionality and risk reduction (risk assessment of the phthalate versus the alternative), also availability and accessibility on the market needs to be considered.

The BRA 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. A plan to perform an update of the relevant part of the technical file of the device needs to be submitted during the certification process (post-market surveillance plan referred to in Article 84, the requirements are set out in Section 1.1 of Annex III MDR) and this should also cover updates needed on the justification for the presence of CMR/ED phthalates.

7. Benefit assessment

These Guidelines do not provide information for the benefit-risk assessment of the use of a medical device itself but are limited to the methodology on how to perform a BRA for the justification of the presence of CMR 1A or 1B and/or ED phthalates in a medical device above 0.1% (w/w).

The evaluation of the overall benefit-risk assessment of a medical device is presented in other documents (e.g. MEDDEV 2.7/1 rev4, EN ISO 14971).

The benefits of the CMR/ED phthalate use in a medical device need to be compared to the benefits of the potential relevant alternatives, with the focus of the analysis being on

the net or incremental benefits of use of the CMR/ED phthalate in comparison to the alternatives. These benefits may include material or clinical benefits. Uncertainties about the estimates or reliability of the data, assumptions, etc. for the parameters need to be presented.

7.1 Material benefit

A medical device does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but may be assisted in its function by such means. For the use of phthalates in medical devices, additional functionalities need to be considered. One of the functionalities is the fine-tuning of the flexibility of PVC when used as plasticisers e.g. in intubation devices. For blood bag materials other requirements are, for example, resistance to heat and chemicals, especially during sterilisation, and permeability of gases to assure that pH and oxygen levels remain stable. In addition, DEHP has an additional property namely the stabilising effect on red blood cells (RBCs) (SCENIHR 2015). A number of alternatives were evaluated as alternative for DEHP in blood bags (Simmchen *et al.*, 2012, SCENIR 2015).

Platelets are extremely sensitive to changes in the pH of the medium in which they are suspended, so sufficient gas permeability to O₂ and CO₂ has to be assured in the containers devoted to their storage (Simmchen *et al.*, 2012). For this reason, DEHP has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) (Simmchen *et al.* 2012, Prowse *et al.* 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also other materials, like polyolefins, are currently used for platelet storage bags (Prowse *et al.* 2014). This potentially will allow the storage of platelet concentrates for up to 7 days, if measures to prevent bacterial contamination can be safely implemented.

It should be noted that the benefit of phthalates in terms of material functionality and performance may differ from device to device. An alternative may be available for one application while this may not be available for another in view of added or specific demands on the functionality of the phthalate.

7.2 Clinical benefits

Clinical benefit of medical devices is defined in the MDR as follows:

'clinical benefit' means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health; (Regulation (EU)2017/745: Article 2 Definitions: (53)):

This "clinical benefit" has to be substantiated by the manufacturers in the "clinical evaluation" of the medical device, which includes a number of considerations. These include a discussion and overall conclusions covering safety and performance results, assessment of risks and clinical benefits, discussion of clinical relevance in accordance

with clinical state of the art, any specific precautions for specific patient populations, implications for the investigational device and limitations of the investigation.

A “clinical benefit” could include any meaningful, measurable, patient-relevant outcome as presented below. SCHEER identified the following examples that may be relevant for the use of phthalates (list not exclusive):

- Improved survival rates
- Improved length of hospital stay
- Improved time of intervention
- Improved time of placing (among others in tubes and catheters)
- Improved product quality/clinical performance (among others in tubes and catheters) in terms of:
 - Improved leakage rates
 - Improved breakage rates
 - Improved knotting rates
 - Improved blockage rates
 - Improved bending performance rates
 - Improved release rates of toxic substances
 - Improved release rates of (nano-)particles
- Improved displacement rates
- Improved possibilities for sterilisation
- Reduction of diameters in relation to performance
- Possibility to produce “multiple-purpose” devices, (e.g. inclusion of additional sensors), and therefore reduction of over-all patient-stress and patient-impact
- Improved observability (safety) in terms of translucence, printability, radiopaque lines included, identifiability, traceability, etc. (among others in tubes and catheters)
- Fewer adverse events, e.g. reduced mucosal or endothelial irritation or injury rates (among others in tubes and catheters)
- Fewer serious adverse events and serious incidents

The benefit of the use of the CMR/ED phthalate should always be judged with respect to the “intended use” of the medical device and the exposed patient-group to the medical device and weighed in its clinical impact (“clinically relevant difference”). These aspects should be judged by clinical experts.

Quantitative information on the benefits should be provided where possible or at a minimum qualitative description of their magnitude. Information on the probability of the benefit to occur and/or the duration of the benefit should also be included.

8. Methodologies for Benefit –Risk Assessment

In general, a Benefit - Risk Assessment (BRA) aims to evaluate the desired effects of therapeutic means, medicines or devices, against their undesired effects, i.e., risks for human health. An appropriate BRA can contribute to a more objective analysis and help conformity verification bodies and authorities towards a more objective and transparent decision-making process. Weighing the benefits and risks can be a complex task. It may involve the evaluation of a large amount of data that should be as accurate as possible,

without methodological weaknesses and biases. There is always some uncertainty around the actual benefits and risks, because they can only be determined by looking at the information that is available at a given point in time which may contain various sources of uncertainty.

For the BRA of medical devices in general, guidance is available in section A7.2. of MEDDEV 2.7/1, revision 4 "Clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC". EN ISO 14971 (FDIS published in 2019) and the accompanying ISO/TR 24971 provide information on the risk benefit analysis to be performed within a risk management process. Additional information may be found elsewhere, for example in the documents of the FDA 2016, 2018,. It should be noted that the acceptability of any risk is weighted against the benefit of the use of the medical device.

Several methodologies for BRA have been proposed (Guo et al, 2010, Mt-Isa *et al.* 2014), of which most methodologies are so far, mainly used for pharmaceutical products. However, it should be underlined that for medical devices the quantitative determination of a benefit-risk ratio may be rather difficult to be made and expressed in a figure. In such cases a qualitative approach of weighing the benefit based on expert judgement might be used. One methodology, namely the multi criteria decision analysis (MCDA), can be generally applied to various areas of BRA. Therefore, this methodology might also be suitable for performing the BRA of medical devices (see Annex 7). The MCDA methodology has its origins in decision theory aiming to evaluate multiple conflicting criteria in decision making. These criteria can include the benefits and risks of the use of a medical device on human health.

The final BRA of both the used CMR/ED phthalate and potential relevant alternatives should contain all aspects as indicated in the framework above. A quantitative or semi-quantitative description of the risks (e.g. MoS, RCR) and of the benefits of a medical device containing a CMR/ED phthalate or alternative should be the basis for a BRA. However, although quantitative approaches for a BRA are preferable, a qualitative description of the value judgements about the balance of benefits and risks might also be an acceptable approach when justified (see step 10).

9. Uncertainty analysis

Uncertainty plays an important role in medical decision making. It is widely accepted that, despite the methodological and technological improvements that were achieved in the past decades, there is never absolute certainty regarding the safety, effectiveness, or performance of a medical treatment or use of a device. Therefore, the degree of certainty and thus uncertainty of the benefits and risks of a medical device is a factor that should always be considered when making BRA.

There are various sources of uncertainty in bio-medical studies; a major source of uncertainty is the biological differences among individuals. Another source of uncertainty is the intra- and inter- variability of the laboratories, with respect to equipment, reagents, and methods used. It is also accepted that diagnostic tools which evaluate benefit and risk share several limitations, giving false negative and false positive results in a variety of cases. Observer variation occurs quite often and should always be taken

into account. Other factors that may influence the degree of uncertainty include: the type of clinical information available (e.g., clinical investigation data, observational studies, evidence derived from registries or use experience), the representativeness of the information (e.g., sample size, relevance of the sample to the referent population exposed to the device), as well as the statistical inferences derived from the information.

A number of techniques for uncertainty analysis are described in the Guidance for Socio-Economic Analysis of ECHA (ECHA 2011). The aim is to determine whether uncertainties in the estimation of impacts could affect the overall conclusions. More accurately, the techniques shown can be used to either reduce the variability of estimates, or to help test whether uncertainties affect the conclusions drawn. The only way to actually reduce uncertainty is through better data, better understanding and knowledge of the uncertainties and through further analysis. However, in most cases residual uncertainties will remain.

Recently EFSA published a guidance on uncertainty analysis (EFSA 2018a) and a description of the principles and methods behind the guidance for uncertainty analysis (EFSA 2018b). The EFSA Guidance recognises that the form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of each analysis and the degree of uncertainty that is present. Therefore it is important to identify appropriate options for each BRA. The EFSA documents provide a flexible framework for uncertainty analysis within which different methods may be selected, according to the needs of each BRA. It seems likely that also for medical devices a similar flexibility is needed in view of the broad range of medical devices used.

EFSA describes a number of main elements of uncertainty that need to be considered in the uncertainty analysis:

EFSA: Main elements of uncertainty analysis

- Identifying uncertainties affecting the assessment. This is necessary in every assessment and should be done in a structured way to minimise the chance of overlooking relevant uncertainties. In assessments that follow standardised procedures, it is only necessary to identify nonstandard uncertainties.
- Prioritising uncertainties within the assessment plays an important role in planning the uncertainty analysis, enabling the assessor to focus detailed analysis on the most important uncertainties and address others collectively when evaluating overall uncertainty. Often prioritisation will be done by expert judgement during the planning process, but in more complex assessments it may be done explicitly using influence analysis or sensitivity analysis.
- Dividing the uncertainty analysis into parts. In some assessments, it may be sufficient to characterise overall uncertainty for the whole assessment directly, by expert judgement. In other cases, it may be preferable to evaluate uncertainty for some or all parts of the assessment separately and then combine them, either by calculation or expert judgement.
- Ensuring the questions or quantities of interest are well-defined. Each question or quantity of interest must be well-defined so that the true answer or value could be determined, at least in principle. This is necessary to make the question or quantity a proper subject for scientific assessment, and to make it possible to express uncertainty about the true answer or value clearly and unambiguously.

Some assessments follow standardised procedures, within which the questions and/or quantities of interest should be predefined. In other assessments, the assessors will need to identify and define the questions and/or quantities of interest case by case.

- Characterising uncertainty for parts of the uncertainty analysis. This is needed for assessments where assessors choose to divide the uncertainty analysis into parts but may only be done for some of the parts, with the other parts being considered when characterising overall uncertainty.
- Combining uncertainty from different parts of the uncertainty analysis. This is needed for assessments where the assessors quantify uncertainty separately for two or more parts of the uncertainty analysis.
- Characterising overall uncertainty. Expressing quantitatively the overall impact of as many as possible of the identified uncertainties, and describing qualitatively any that remain unquantified. This is necessary in all assessments except those standardised assessments where only standard uncertainties are identified (e.g. inter-and intra-species uncertainty factors).
- Prioritising uncertainties for future investigation. This is implicit or explicit in any assessment where recommendations are made for future data collection or research, and may be informed by influence or sensitivity analysis.
- Reporting uncertainty analysis. Required for all assessments, but extremely brief in standardised assessments where only standard uncertainties are identified.

A number of methods that can be used in the uncertainty analysis include:

- Sensitivity analysis
- Scenario analysis
- Expert judgement
- Monte Carlo Simulations

Some of these techniques can be used in combination (e.g. scenario analysis together with expert judgement to establish ranges for key variables) but also together with less commonly used techniques such as risk-risk analysis, Delphi techniques and portfolio analysis, which can be used to help reduce the variability of estimates but are not discussed in these Guidelines.

After performing the uncertainty analysis, the observed overall confidence associated with a BRA can be expressed as a probability score. This score gives the risk assessor an indication what the uncertainty is in the BRA.

In situations where sufficient data are available, a quantitative categorisation of probability levels is preferred. If this is not possible, the manufacturer should give a qualitative description. A good qualitative description is preferable to an inaccurate quantitative description (EN ISO 14971).

EFSA (EFSA, 2018b) and SCHEER (2018) use a rather detailed probability scale of 9 and 7 probability levels, respectively. EFSA stresses that this scale may be used as an aid to support the development of judgements and that other ranges or qualitative descriptions can be used as well. EFSA (2018b) also argues that presenting the numerical probabilities alongside verbal expressions of probability, e.g. 'Likely (> 66% probability)', increases the consistency of interpretation.

A detailed scale does not seem to be applicable for the uncertainties that can be obtained during a BRA evaluation of medical devices. For medical devices, a probability scale as indicated in Table 2 may be used EN ISO showing a 5-level scale recommended by ISO for semi-quantitative assessments (EN ISO 14971, Table D4). Table 2 further shows the verbal terms and subjective probability ranges that are based on a simplification of the EFSA/SCHEER scales.

Table 2: Probability scale for (semi-)quantitative description of the overall confidence

ISO probability term	Subjective probability range	Probability term
Frequent	> 90%	very likely
Probable	66-90%	likely
Occasional	33-66%	as likely as not
Remote	10-33%	unlikely
Improbable	<10%	very unlikely

10. Conclusions

These Guidelines are intended to be used for a BRA 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. The Guidelines can be used for the justification of the use of CMR/ED phthalates in a medical device according to the Regulation (EU) 2017/745 on medical devices. 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. Major aspects include the functionality of phthalates, the performance of the medical device using the phthalate or the potential relevant alternative for the phthalate, as well as the risk assessment of the phthalate or the alternatives. In the end, the benefit(s) shall be weighed against the possible risks of the use of the CMR/ED phthalate and of the alternative substance, materials, designs or medical treatments. This overall analysis will determine whether it is justified or not to use a CMR/ED phthalate in a medical device.

In view of the concern of the CMR/ED properties of phthalates, further research to possibilities to replace these phthalates in medical devices is highly encouraged by the SCHEER.

During the preparation of these Guidelines for BRA of the use of CMR/ED phthalates in medical devices, SCHEER noticed that a number of BRA methodologies are theoretically available. However, there is a considerable lack of data 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. As the BRA of the presence of phthalates may have an impact on the conclusions of the "overall" benefit-risk determination of the medical device, a periodic update of the BRA of the medical device may be needed. 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. A plan to perform an update of the general BRA for the medical device should be included in the dossier before marketing the device, and this should also include a plan regarding the necessary updates on the evaluation of alternatives for CMR/ED phthalates.

Pending on new scientific evidence, it is recommended to evaluate the use and usefulness of these Guidelines after an application period of three years.

11. Consideration of the responses received during the public consultation process

A public consultation on these Guidelines was opened on the website of the non-food scientific committees from 18 March to 29 April 2019. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders. A total of 197 submissions from 19 contributors (providing 378 comments and additional references) provided input to different chapters and subchapters of the document. The vast majority of comments came from industry and were requesting clarifications. Each submission was carefully considered by the SCHEER and the scientific opinion has been revised to take account of relevant comments. The literature has been accordingly updated with relevant publications. The SCHEER expresses their thanks to all contributors for their comments and for the literature references provided during the public consultation. The text of the comments received and the response provided by the SCHEER is available at:

https://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scheer_consultation_08_en

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C. ANNEXES

Annex 1: SCHEER mandate on benefit-risk assessment on the use of CMR/ED phthalates

1. Background

What are phthalates?

Phthalates are the esters of 1,2-benzenedicarboxylic acid (o-phthalic acid) and their chemical structure consists of one benzene ring and two ester functional groups linked with two consecutive carbons on the ring¹⁰. The hydrocarbon chains of the ester groups are either straight or branching; they give each substance its name and they are responsible for the different properties among phthalates. Phthalate esters (PEs) may be categorised into three distinct groups according to the length of their carbon chain. High molecular weight (HMW) phthalates include those with 7–13 carbon atoms in their carbon chain and low molecular weight (LMW) those with 3–6 carbon atoms in their backbone. DEHP is classified as a LMW phthalate. A third group includes dimethyl phthalate (DMP) and diethyl phthalate (DEP)¹¹.

What are they used for?

Phthalates are widely used in industry as plasticisers of polymers such as polyvinyl chloride (PVC). HMW phthalates are used in a variety of applications such as coated fabrics and roofing membranes. LMW phthalates are used in medical devices, adhesives, paints, inks and enteric-coated tablets. DEHP is the most widely used phthalate in medical devices. DMP and DEP are not used as plasticisers but e.g. as additives in cosmetics, medical devices, and household products.

Potential CMR or endocrine-disrupting properties

The interaction of phthalates with the polymers they are embedded in is weak, so they may migrate from the plastic product into the environment and into the human body if the product is in contact with it.

Correlation between exposure to a range of phthalates and adverse health effects has been documented in animals and humans (see for example tables in Mariana *et al.* 2016 and Katsikantami *et al.* 2016). A number of phthalates are suspected of and/or have been classified or identified as having CMR or endocrine-disrupting properties.

¹⁰ A global assessment of phthalates burden and related links to health effects. Katsikantami et al., Environ Int. 2016 Dec;97:212-236. <https://www.ncbi.nlm.nih.gov/pubmed/?term=katsikantami>

¹¹ Footnote added by SCHEER. It should be noted that there are hundreds of phthalates of which only a limited number is used as plasticiser in polymers. Phthalates can be categorised according to the length of the carbon chain and one of these categorisations is mentioned in the mandate of DG GROW.

Previous work of Commission Scientific Committees on phthalates

Previous opinions on the most commonly used phthalate DEHP [di-(2-(ethylhexyl) phthalate)] in medical devices were issued by EU Scientific Committees in 2002 (SCMPMD), 2008 and 2015 (SCENIHR). The 2008 Opinion concluded that *"So far, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans"*, but noted that *"newborn and pre-term born male infants are of special concern"*. In the 2015 Opinion, SCENIHR additionally identified that *"patients subject to haemodialysis procedure may be at risk of DEHP induced effects"*. The Committee noted that *"Food is the primary source of exposure to DEHP for the general population."*

In both opinions, the Committee emphasised that *"the benefit of the medical devices must also be considered"* and in the 2008 Opinion the Committee states that *"each alternative to DEHP, however, must also be evaluated with regard to their functionality in respect to medical devices. The risk and benefits of using alternative plasticizers should be evaluated case by case."* In the 2015 opinion, the Committee states that *"The potential for replacement of DEHP in these products should be considered against their efficiency in the treatment, as well as the toxicological profile and leaching properties of the alternative materials."*

The legal obligation

Article 5 paragraph 2 of the Regulation 2017/745 on medical devices stipulates: *"A device shall meet the general safety and performance requirements set out in Annex I which apply to it, taking into account its intended purpose."*

Accordingly, Section 10.4 of Annex I, which deals with substances in medical devices, states that *"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."* Particular substances of concern are those which (a) are carcinogenic, mutagenic or toxic to reproduction (CMR), of category 1A or 1B,¹² or (b) have endocrine-disrupting properties (ED)¹³. The Regulation states that:

"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"*

¹² in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008

¹³ identified as such in accordance with the relevant provisions of Regulation (EC) No 1907/2006 or respectively of Regulation (EU) No 528/2012

shall only contain any such substance above the concentration of 0.1% weight by weight where justified pursuant to Section 10.4.2. The justification shall be based on several elements, including the latest relevant scientific committee guidelines on benefit-risk assessment of the presence of such substance in devices.

According to Section 10.4.3, the Commission shall provide a mandate to the relevant scientific committee to prepare such guidelines for phthalates which are subject to these provisions. These guidelines are explicitly requested by the Regulation to be available at the latest on the date of application of the Regulation, and are to be updated whenever appropriate on the basis of the latest scientific evidence, or at least every five years.

2. Terms of reference

The Scientific Committee is requested to provide guidelines on the benefit-risk assessment of the presence, in the medical devices specified below, of phthalates which have one or more of the following properties: carcinogenic, mutagenic, toxic to reproduction or endocrine-disrupting, according to the criteria outlined in the previous section.

The devices covered, or those parts thereof of those materials used therein, are those which:

- 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.

The guidelines shall include guidance on how, for an individual device, to:

- analyse and estimate potential patient or user exposure to the substance,
- analyse possible alternative substances, materials, designs, or medical treatments,
- to justify 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.

In addition, the Scientific Committee is requested to:

- identify any relevant knowledge gap, and
- to give consideration to what extent of new evidence would be deemed appropriate to justify an update of these guidelines before the maximum period of five years.

In order to ensure the appropriateness of this guidance the Scientific Committee should *inter alia*:

- involve at the appropriate level the notified bodies active in the field of medical devices, or other relevant stakeholders such as Competent Authorities, professional and patient associations, industry associations, while maintaining scientific independence,
- involve to the necessary extent the relevant EU Agencies and Scientific Committees.

Annex 2: Medical Device Regulation (Regulation 2017/745) on CMR and/or ED substances

The requirement for justification of the presence of CMR 1A or 1B and/or ED hazardous substances is described in Annex I 10.4.2 as presented in the text box below.

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.

Annex 3: Definitions/descriptions – References - Glossary

Definitions (Regulation (EU) 2017/745)

Benefit-risk determination: means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer.

Performance: means the ability of a device to achieve its intended purpose as stated by the manufacturer.

Clinical performance: means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

Clinical benefit: means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.

Risk: means the combination of the probability of occurrence of harm and the severity of that harm.

Adverse event: means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Serious adverse event: means any adverse event that led to any of the following: (a) death, (b) serious deterioration in the health of the subject, that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalisation or prolongation of patient hospitalisation, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (v) chronic disease, (c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

Incident: means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

Serious incident: means any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat.

Serious public health threat: means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

Device deficiency: means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Regulation (EU) 2017/745 Annex XIV Clinical evaluation and post-market clinical follow-up. Part A "Clinical evaluation" Section 3 describes the characteristics that shall be considered for demonstration of equivalence.

"A clinical evaluation may be based on clinical data relating to a device for which equivalence to the device in question can be demonstrated. The following technical, biological and clinical characteristics shall be taken into consideration for the demonstration of equivalence:

Technical: the device is of similar design; is used under similar conditions of use; has similar specifications and properties including physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms; uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements;

Biological: the device uses the same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables;

Clinical: the device is used for the same clinical condition or purpose, including similar severity and stage of disease, at the same site in the body, in a similar population, including as regards age, anatomy and physiology; has the same kind of user; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.

The characteristics shall be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Considerations of equivalence shall be based on proper scientific justification. It shall be clearly demonstrated that manufacturers have sufficient levels of access to the data relating to devices with which they are claiming equivalence in order to justify their claims of equivalence.”

Definitions on assessment of alternatives (OECD Toolbox Glossary)

Note: The term "chemical" is used synonymously with "substance"

Alternatives assessment: A process for identifying and comparing potential chemical and non-chemical alternatives that can be used as substitutes to replace chemicals or technologies of high concern¹

Chemical substitution: The process of replacing a chemical of concern with a safer chemical, material or product, or technology/process that eliminates the need to use that chemical

Cost/benefits and availability: The negative (cost) and positive (benefit) implications, direct and indirect, resulting from some action. This includes both financial and non-financial information. Availability refers to the production of an alternative and its market accessibility³

Functional use approach: This approach starts with identifying the function that is desired. The concept is applied in two ways: first and foremost, to characterise the purpose a chemical or mixture serves, or the properties it imparts in a product or process (functional use), and second, to evaluate the function of the product and how its use may influence the assessment of alternatives^{4, 5}

Material substitution: The process of replacing a material containing a chemical of concern with a safer chemical, material, product or technology/process that eliminates the need to use that chemical

Mixture: A composition of at least two chemicals in which they do not react⁶

Technical feasibility: The determination as to whether the performance or functional requirements of a chemical, material or product could be fulfilled or replaced by eliminating or using an alternative chemical, material, product, process or technology, while considering any need for process adaptations and changes³

Process modification: Changes in manufacturing processes to eliminate, reduce or substitute chemicals of concern. Such changes may include synthesis pathways, waste reduction, and manufacturing procedures where chemicals are used.

Product performance: The ability of a product to meet identified performance requirements. The boundaries of performance characteristics are defined by the user³

Product substitution: The process of replacing a product containing a chemical of concern with a chemical, material or product or technology/process that eliminates, reduces or substitutes the need to use that chemical.

¹ Adapted from *Alternatives Assessment Guide, version 1.0*. 2013. Interstate Chemicals Clearinghouse.

² REACH. Title I, Chapter 2, Article 3.

³ Current Landscape of Alternatives Assessment Practice: A Meta-Review. Organisation for Economic Cooperation and Development. 2013.

⁴ U.S. EPA. 2006. National Pollution Prevention and Toxics Advisory Committee (NPPTAC) Recommendation to the EPA Administrator and Deputy Administrator on Incorporating the Functional Use Approach into OPPT Activities.

⁵ Lavoie, E. T., *et al.* 2010. "Chemical Alternatives Assessment: Enabling Substitution to Safer Chemicals." *Environmental Science & Technology* 44(24): 9244-9249.

⁶ Adapted from *U.N. Global Harmonized System of Classification and Labelling of Chemicals*. 2003.

⁷ ECHA, 2008. Guidance on Socio-Economic Analysis - Restrictions.

⁸ Adverse event means pre-clinical and clinical occurrences of an effect whereas incident indicates a clinical effect occurring during post-market surveillance.

References

- ECHA (2011) Guidance on the preparation of socio-economic analysis as part of an application for authorisation, European Chemicals Agency 2011.
- EFSA (2019) Draft update of the risk assessment of di-butylphthalate 1 (DBP), butyl-benzyl-phthalate (BBP), bis(2-2 ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) 3 and di-isodecylphthalate (DIDP) for use in food contact 4 materials <http://www.efsa.europa.eu/en/consultations/call/190221>.
- Guo JJ, Pandey S, Doyle J, Bian B, Lis Y, Raisch DW. A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. Value Health. 2010;13(5):657-66.

Glossary

BBP	Benzylbutylphthalate
BMD	Bench Mark Dose
BRA	Benefit-Risk Analysis
BTHC	Butyryl-tri-n-hexylcitrate
CAS	Chemical Abstracts Service
CEN	European Committee for Standardization
CLP	Classification Labelling and Packaging regulation (EC No 1272/2008)
CMR	Carcinogenic, Mutagenic, toxic to Reproduction (Reprotoxic)
DBP	DiButylphthalate,
DCHP	Dicyclohexylphthalate
DEHP	Diethylhexylphthalate
DIBP	Diisobutylphthalate
DIDP	Di isodecyl phthalate)
DINCH	1,2- cyclohexanedicarboxylic acid, diisononyl ester)
DINP	Di isononyl phthalate)
DIPP	Diisopentylphthalate
DMEP	Bis(2-methoxyethyl)phthalate
DNHP	Dihexylphthalate
DHNUP	1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters
DPP	Dipentyl phthalate
DMEL	Derived Minimum Effect Level
DNEL	Derived No Effect Level
EC	European Commission
ECB	European Chemicals Bureau (now ECHA)
ECHA	European Chemicals Agency (formerly ECB)

ED	Endocrine Disruptor
EEC	European Economic Community
EMA	European Medicines Agency
EFSA	European Food Safety Authority
EN-ISO	CEN and ISO combined published document
FDA	Food and Drug Administration (USA)
FDIS	Final Draft International Standard
ISO	International Organization for Standardization
LOAEL	Lowest Observed Adverse Effect Level
MCDA	Multi Criteria Decision Analysis
MDD	Medical Device Directive (Council Directive 93/42/EEC)
MDR	Medical Device Regulation (EU 2017/745)
MoA	Mode of Action
MoE	Margin of Exposure
MoS	Margin of Safety
NICU	Neonatal Intensive Care Unit
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Cooperation and Development
PoD	Point of departure
PVC	Polyvinyl chloride
RBC	Red Blood Cell
RCR	Risk Characterisation Ratio
REACH	Registration, Evaluation, Authorisation and restriction of CHemicals.
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
T25	25 % increase of the tumour rate over controls
TDI	Tolerable Daily Intake
TE	Tolerable Exposure (EN ISO 10993-17:2002 in mg/day)
TEHTM	Tri(2-ethyl hexyl)trimellitate also TOTM Trioctyltrimellitate
TI	Tolerable Intake
TOTM	Trioctyltrimellitate also TEHTM Tri(2-ethyl hexyl)trimellitate
TWI	Tolerable Weekly Intake

Annex 4: CMR and/or ED substances

CMR substances are substances identified and classified as carcinogenic, mutagenic or toxic for reproduction of different categories based on the intrinsic toxic properties of a substance for which categories 1A and 1B apply to these Guidelines. In Europe, classification for these endpoints is harmonised through harmonised classification and labelling (CLH). Details can be found at <https://echa.europa.eu/regulations/clp/understanding-clp>. For a specific substance to be classified as CMR 1A, 1B or 2 a dossier needs to be prepared and if the Commission finds that the proposed classification is appropriate, it submits a draft decision concerning the inclusion of that substance in Part 3 of Annex VI to the CLP Regulation (Regulation (EC) 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures).

- Category 1A means that the substance is a known human carcinogen, mutagen or reproductive toxicant based on human evidence.
- Category 1B means that the substance is a presumed human carcinogen, mutagen or reproductive toxicant based on animal studies.
- Category 2 means that a substance is considered as suspected carcinogen, mutagen or reproductive toxicant based on limited evidence from animal studies or humans (not part of these Guidelines).

Documents on the classification are publicly available, and a tutorial to search entries is given here:

http://www.chemsafetypro.com/Topics/EU/Annex_VI_to_CLP:_List_of_Harmonised_Classification_and_Labelling_for_Certain_Hazardous_Substances.html

Guidance for the identification of endocrine disruptors (ED) in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 has been published on 7th June 2018 by ECHA and EFSA (doi: 10.2903/j.efsa.2018.5311; EFSA Journal 2018;16(6):5311) which can be accessed via:

<https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311>

This EFSA/ECHA Guidance describes when a substance shall be considered as having endocrine disrupting properties.

"A substance shall be considered as having endocrine disrupting properties if it meets all of the following criteria:

- a) it shows an adverse effect in [an intact organism or its progeny]/[non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population⁶ that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;*
- b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;*
- c) the adverse effect is a consequence of the endocrine mode of action.*

It should be highlighted that the 'endocrine mode of action' as stated in point (b) should be interpreted as 'endocrine activity' while the term 'endocrine mode of

action' in point (c) covers the link between the adverse effect and the endocrine activity identified in points a) and b), respectively.

Keeping this in mind point (b) above should be understood as (differences from above in *italics*):

it shows *endocrine* activity, i.e. it *has* the potential to alter the function(s) of the endocrine system;

Consequently point (c) above should be understood as (differences from above in *italics*):

the substance has an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the adverse effect and the endocrine activity."

EDs identified with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), will finally enter the REACH candidate list of substances of very high concern for potential inclusion in REACH Annex XIV. The information can be found in the respective decision document accessible via: <https://echa.europa.eu/candidate-list-table>.

For substances having endocrine-disrupting properties as indicated above, there is currently no information concerning whether it is foreseen to publish them in central lists or annexed to a Regulation.

EDs identified by the delegated act pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products, can be accessed through the Biocidal Products Committee opinions on active substance approval which can be accessed via ECHA's website (<https://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval>).

Substances undergoing an ED assessment under the REACH or Biocidal Products regulations that have been brought for discussion to ECHA's ED Expert Group are included in ECHA's endocrine disruptor (ED) assessment list: <https://echa.europa.eu/ed-assessment>. For each substance, the table shows the assessing or evaluating Member State (submitter), the outcome and the suggested follow-up for the assessment, and the date of the latest update to the list entry.

Recently the Commission Implementing Decision (EU) 2017/1210 was published that identified some phthalates (Bis(2-ethylhexyl) phthalate (DEHP), Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP) and Diisobutyl phthalate (DIBP)) as substances of very high concern due to their endocrine disrupting properties with probable serious effects to humans (European Commission 2017).

<https://publications.europa.eu/en/publication-detail/-/publication/357b3d45-620f-11e7-9dbe-01aa75ed71a1/language-en/format-PDF>

For completeness, even if not relevant for the purpose of this guidelines, Bis(2-ethylhexyl) phthalate (DEHP) was also identified in 2014 as a substance of very high concern due to its endocrine disrupting properties with probable serious effects to the environment.

In addition, Commission Implementing Decision (EU) 2018/636 identified Dicyclohexylphthalate (DCHP) as substance of very high concern (SVHC) according to Article 57(f) of REACH Regulation (EC) 1907/2006, due to its endocrine disrupting

properties with probable serious effects to humans. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0636&from=EN>

Annex 5: Legislation on CMR and/or ED phthalates

Due to their reprotoxic properties and additionally since 2014 for DEHP due to their endocrine disrupting properties for the environment and since 2017 for DEHP, BBP, DBP, and DIBP due to their endocrine disrupting properties for human health, a considerable number of phthalates have been identified as substances of very high concern (SVHC) and therefore included in the candidate list for the inclusion in Annex XIV of the REACH regulation (Annex XIV of REACH EC 1907/2006, see <https://echa.europa.eu/de/candidate-list-table> for the most recent update of the candidate list).

Eight phthalates are also listed on the Authorisation list (Annex XIV of REACH), namely DEHP, BBP, DIBP, DBP, DIPP (diisopentylphthalate), Bis(2-methoxyethyl) phthalate, dipentyl phthalate, and N-pentyl-isopentylphthalate. Since February 2015 DEHP, BBP, DIBP, and DBP cannot be used within the European Union without authorisation. The same provision would apply to the remaining four phthalates on Annex XIV from July 2020. To date, applications for authorisation have been submitted for DEHP and DBP only. However, imported articles do not come under the authorisation requirement. For the purpose of evaluating applications for authorisation, the ECHA Committee for Risk Assessment (RAC) has developed reference DNELs for several substances, including DEHP, BBP, DBP, and DIPP. (See Evaluating Applications table/Reference DNELs on ECHA's website:

<https://echa.europa.eu/applying-for-authorisation/evaluating-applications>.)

Risks to human health arising from the use of an Annex XIV substance in medical devices regulated by Directives 90/385/EEC, 93/42/EEC or 98/79/EC are exempted from authorisation requirements under Title VII of the REACH Regulation¹⁴. ECHA is currently preparing a recommendation on the inclusion of the ED properties for environment for DEHP in Annex XIV to REACH.¹⁵ If DEHP is included on Annex XIV for environmental hazards, applications for authorisations may need to be prepared for uses of the substance in medical devices in the future.

REACH Annex XVII (entry 51) also restricts the placing on the market of articles containing DEHP, BBP, DBP, and DIBP in concentration greater than 0.1% weight by weight of the plasticised material, individually or in combination in a range of articles. These articles include toys¹⁶ and childcare articles, as well as other primarily consumer and professional use articles which lead to dermal or inhalation exposure. (For risk assessment conclusions, including derivation of a DNEL for DIBP, see Compiled RAC & SEAC opinion and background document on ECHA's website: <https://echa.europa.eu/previous-consultations-on-restriction-proposals/-/substance-rev/13919/term>.)

¹⁴ These Regulations will be replaced by:

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

¹⁵ <https://echa.europa.eu/draft-recommendation-for-amendment-of-authorisation-list-entries-previous-consultation>

¹⁶ The Toy Safety Directive (2009/48/EC) stipulates that chemicals that are susceptible to cause cancer, change genetic information, harm fertility or harm an unborn child (CMR substances) are no longer allowed in accessible parts of toys beyond the concentration limits set in the CLP Regulation ((EC) No 1272/2008).

REACH Annex XVII (entry 52) restricts the placing on the market and the use of DINP, DIDP, and DNOP, as a substance or in mixture, in concentrations greater than 0.1% weight by weight of the plasticised material in toys and childcare articles which can be placed in the mouth of children. In 2010, the European Commission requested ECHA to review the scientific evidence on the risks posed by articles containing these phthalates with the view to conclude on the need or not for further actions under REACH. The report and RAC risk assessment conclusions (including information on the derivation of DNELs) can be found on ECHA's website: <https://echa.europa.eu/consultations-draft-review-report-previous-consultations/-/substance-rev/1108/term>.

EFSA recently launched a consultation on its updated 2005 risk assessments of DBP, BBP, DEHP, DINP and DIDP which are authorised for use in plastic FCM, by using the same database as ECHA for its 2017 assessment of certain phthalates. The draft update of the risk assessment can be found here:

<http://www.efsa.europa.eu/en/consultations/call/190221>

In addition to the REACH legislation, there is also product-specific legislation which regulates certain phthalates, i.e. the Cosmetic Products' Regulation (EC/1223/2009) and the Regulation on materials and articles intended to come into contact with food (Food Contact Materials, Regulation EC 1935/2004, as general framework regulation and Regulation EU 10/2011 specific for plastic materials and articles destined to be in contact with foodstuffs, recently amended by Regulation 2018/831). Both in the MDD (93/42/EEC) and the more recent MDR (2017/745), phthalates are specifically mentioned for their use in medical devices.

For a number of phthalates there is legislation available that might contain information relevant for the use of phthalates in medical devices. Of specific relevance for medical devices may be the Regulation EU 10/2011, which also includes provisions for the use of phthalates in food contact materials and articles with respect to migration limits. This may be a parallel with migration (and thus potential internal exposure) of phthalates as present in polymers used for medical device manufacturing. In Annex I of the Regulation EU 10/2011 all substances are listed, which are authorised for the use as starting material or additive for plastic layers in plastic materials and articles. Each substance must not exceed its specific migration limit (SML). The following phthalates and other plasticisers¹⁷ are authorised for use as additives:

DBP (SML) = 0.3 mg/kg food

only to be used as:

- (a) plasticiser in repeated use materials and articles in contact with non-fatty foods;
- (b) technical support agent in polyolefins in concentrations up to 0.05% in the final product

BBP, SML = 30 mg/kg food

Only to be used as:

- (a) plasticiser in repeated use materials and articles;

¹⁷ Not exhaustive examples for other than phthalates

(b) plasticiser in single-use materials and articles in contact with non-fatty foods, not for contact with infant formulae and follow-on formulae (Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children (Directive 2006/125/EC);

(c) technical support agent in concentrations up to 0.1% in the final product.

DEHP, SML = 1.5 mg/kg food

Only to be used as:

(a) plasticiser in repeated use materials and articles in contact with non-fatty foods;

(b) technical support agent in concentrations up to 0.1% in the final product.

DINP SML = 9 mg/kg food (cumulative with DIDP)

only to be used as

(a) plasticiser in repeated use materials and articles;

(b) plasticiser in single-use materials and articles in contact with non-fatty foods, not for contact with infant formulae and follow-on formulae (Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children (Directive 2006/125/EC)

(c) technical support agent in concentrations up to 0.1% in the final product.

DIDP, SML = 9 mg/kg food (cumulative with DINP)

Only to be used as

(a) plasticiser in repeated use materials and articles;

(b) plasticiser in single-use materials and articles in contact with non-fatty foods, not for contact with infant formulae and follow-on formulae (Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children (Directive 2006/125/EC)

(c) technical support agent in concentrations up to 0.1% in the final product.

Furthermore, for certain plasticizers listed in Regulation (EU) 10/2011, including a number of phthalates, applies a group restriction (Group restriction number 32), that is, the sum of these substances must not exceed an SML of 60 mg/kg foodstuff.

DEHP, BBP, DBP and DIBP must not be contained in homogenous materials above the concentration of 0.1% w/w from July 2019 on according to the Restriction of Hazardous Substances Directive in electrical and electronic equipment RoHS2 (2011/65/EC). For medical devices and *in vitro* diagnostic products this restriction takes effect in July 2021.

Table 1 CMR Classification^{*)} and ED designation^{)} of phthalates** (status Jan 2019)

Phthalate	Abbreviation	CAS number	CMR Classification*	ED identification**
bis(2-methoxyethyl)phthalate	DMEP	117-82-8	Repr 1B	-
bis(2-ethylhexyl)phthalate	DEHP	117-81-7	Repr 1B	ED
dibutyl phthalate	DBP	84-74-2	Repr 1B	ED
1,2-benzenedicarboxylic acid, dipentylester, branched and linear		84777-06-0	Repr 1B	-
n-pentyl-isopentylphthalate	PIPP	No CAS 776297-69-9?	Repr 1B	-
di-n-pentyl phthalate	DnPP	131-18-0	Repr 1B	-
diisopentylphthalate	DiPeP	605-50-5	Repr 1B	-
benzyl butyl phthalate	BBP	85-68-7	Repr 1B -	ED
diisobutylphthalate	DIBP	85-69-5	Repr 1B	ED
dihexylphthalate	DHP	84-75-3	Repr 1B	
dicyclohexylphthalate	DCHP	84-61-7	Repr 1B	ED

*) as indicated in Annex VI to CLP_ATP10 (in force from 1 December 2018).

**) according to the ECHA Candidate List of substances of very high concern for Authorisation published in accordance with Article 59(10) of the REACH Regulation <https://echa.europa.eu/candidate-list-table>

As substances of concern, knowledge on the exposure to phthalates is important and biomonitoring of populations provides important information. For some of the phthalates already human biomonitoring assessment values, namely Biomonitoring equivalents (BE) or human biomonitoring (HBM) values, have been derived – these are concentrations of biomarkers (metabolites) in urine, which reflect an acceptable chronic exposure, since the basic assumption is an equilibrium between external exposure and internal burden (Angerer *et al.* 2011, Apel *et al.* 2017). In the course of the work done within the HBM4EU project, Human Biomonitoring Guidance Values (HBM-GVs) could be derived for DEHP and DINCH (see HBM4EU Deliverable D5.2, <https://www.hbm4eu.eu>). In addition, HBM-GVs for the following SVHC phthalates are finalised in September 2019 (Deliverable D5.6) and will also be published on the website: BBzP, DiBP, and DnBP.

Annex 6: Use of phthalates in medical devices

Phthalates are abundantly used in polyvinyl chloride (PVC) medical devices such as blood bags, intravenous bags, nutrition pockets, tubing, catheters, respiratory masks or disposable gloves. More than 40% of all plastic-based disposable medical devices are made from PVC. Di-2-ethylhexyl phthalate (DEHP) has been for many years the most commonly used phthalate ester plasticiser in medical devices. A survey among the Danish Medical Device Industry found that 95% of the products contained DEHP [Huntley P, editor The classified phthalates should be phased out of medical devices. Alternatives to Classified Phthalates in PVC Medical Devices Conference; 2014 Mar 27; Copenhagen, Denmark].

Safety concerns have been expressed for several high-risk patients groups, such as neonates, infants, pregnant and breast-feeding women exposed to DEHP. The SCENIHR in its Opinion of 2015 indicated that “a lack of evidence of causation between DEHP-PVC and any disease or adverse effect does not mean that there are no risks”. This lack of evidence applies to all phthalates classified as CMR and/or identified as ED. Therefore the requirement of patient subgroup analysis for the target patient groups as defined in the “Intended Use” of a medical device is now included in the Regulation (EU) 2017/745.

For the use of DEHP, high risk groups were identified including patients undergoing haemodialysis, extracorporeal membrane oxygenation (ECMO), and prematurely born infants in Neonatal Intensive Care Units (NICU), (SCENIHR 2015). The actual exposure of such patient groups relative to the toxicity including CMR/ED property needs to be determined. However, even if the remaining risk is high, the benefit of the treatment should be considered as well. It might be useful to evaluate the patient subgroups separately:

- Paediatric Population (see subgroups)
- Peripubertal males
- Pregnant women
- Breast-feeding women
- any other patient group considered particularly vulnerable or exposed to high levels of phthalates.

For purposes of this Guideline, the following ranges of paediatric subpopulations are proposed to be used as a guide for manufacturers in medical devices (ref. SCCS Notes of Guidance – SCCS/1602/18, section 3-6.9.1, page 78¹⁸)

¹⁸ https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf

Definition of Paediatric Population Subgroups

Paediatric Subgroup	Approximate Age Range
Full-term neonate	<1 week
Newborn	1 week–2 months
Early infant	2–6 months
Crawlers/toddler	6 months–2 years
Preadolescent	2–12 years
Adolescent	12–18 years

In view of ED activity, additional (paediatric) subpopulations may need to be considered including:

- very low birth weight describes newborns less than 1.5 Kg
- low birth weight describes newborns less than 2.5 Kg
- preadolescent age group typically ranges from 11 to 13 years.
- peripubertal males or females

It should be realised that the benefit of medical devices including the use of phthalates must also be considered: The survival of prematurely born infants often depends on the availability of the same medical devices that result in a relatively high phthalate content exposure due to treatment. Whenever possible, material with low release potential should be used (see SCENIHR opinion 2015).

Besides the direct patient benefits of the treatment with a medical device containing phthalates, other functionalities may also need to be considered. For example, DEHP has a stabilising effect on red blood cells (RBCs). RBCs have increased survival rates when stored in DEHP containing blood bags. DEHP is incorporated into the cell walls of RBCs and stabilises the membrane integrity of the RBCs. This results in a prolonged shelf life and thus patient availability of blood stored in DEHP containing blood bags (SCENIHR 2015). A maximum limit of extractable DEHP of 15 mg/100 mL for flexible PVC containing DEHP is indicated in EN ISO 3826-1 on containers for the collection of human blood and blood components.

The plasticiser industry has been investing and developing alternatives to DEHP in medical devices. Today, other plasticisers such as Di-isononyl cyclohexanoate (DINCH, CAS 166412-78-8), Tri-2-ethylhexyl trimellitate (TEHTM, CAS 3319-31-1), butyryl tri-n-hexyl citrate (BTHC, CAS 102818-95-1) and Dioctyl Terephthalate (DOTP, CAS 6422-86-2) are being proposed in medical applications such as medical tubing and blood bags. <https://www.plasticisers.org/applications/medical-applications/>

In conclusion, for any BRA on the use of phthalates and the development of alternatives in medical devices, careful consideration should be used to appropriate patient subgroup analysis regarding medical device use and the resulting potential exposure.

Reference

Huntley P, Editor. The classified phthalates should be phased out of medical devices. Program Meeting on Alternatives to Classified Phthalates in PVC Medical Devices Conference; 2014 Mar 27; Copenhagen, Denmark.

<https://pvc.dk/wp-content/uploads/2016/02/pvc-alternativer-til-klassificerede-ftalater-program.pdf>

Annex 7: Approaches for Benefit-Risk Assessment

Several approaches for BRA have been proposed especially in the context of medicinal products. The Innovative Medicines Initiative PROTECT Project (www.imiprotect.eu), presented a detailed review of approaches used for BRA (Mt-Isa *et al.* 2014). In this review, a large number of approaches were identified and classified as descriptive (qualitative or semi-qualitative) or quantitative frameworks (relying on quantitative methods of trading risks and benefits following mathematical principles), metrics (measures for benefits and risks that are usually endpoint specific), estimation techniques (i.e., simulation techniques and meta-analysis), and utility survey techniques (to elicit stakeholders' preferences).

Concerning quantitative frameworks, according to the European Medicines Agency (EMA) Project Report (EMA/227124/2011), there is no agreement on any one approach to be used in regulatory submission on the benefits and risks of medicines. However, EMA has encouraged the use of quantitative frameworks in regulatory submissions of applications for marketing authorisation of medicinal products.

Although there is little experience with quantitative frameworks in the area of medical devices, some of the BRA approaches used for pharmaceuticals may also be relevant for medical devices and particularly regarding the use of CMR/ED phthalates. In particular, approaches based on multicriteria decision analysis (MCDA) have attracted much attention during the past years in the field of medical decisions. For an introduction to MCDA see Dodgson *et al.* (2009).

In brief, MCDA is based on decision theory and belongs to the general class of multi-criteria analysis models that accommodate decision making with multiple objectives. The main purpose of MCDA is to bring together evaluations of options on different criteria into one overall evaluation. The starting point for MCDA approaches includes identification of the alternatives and the criteria against which the alternatives are appraised. MCDA includes weighting, which ensures that the units of value on all the criteria are comparable so that benefits and risks can be compared by using a common unit of value. In this way, the added value of benefits can be compared to the loss of value from the risks. A number of different weighting methods can be used, ranging from precise elicitation of weights, to weights based on qualitative judgements or including uncertainty.

A generic framework for conducting an MCDA can be based on the steps of the PROACT-URL framework (Hammond *et al.*, 1999), as presented below. A detailed description of the different implementations of MCDA techniques is beyond the scope of this guideline. The chosen techniques and analyses should be presented and justified among others on the basis of internal consistency, logical soundness and transparency.

STEP	Description and relation to framework for Benefit-Risk Assessment described in section A of the Guidelines
Problem	Describe the medical device, its intended use, and the therapeutic context; frame the decision problem in terms of potential alternatives to CMR/ED phthalate. See Step 1: Description and characterisation of the composition of the medical device; and Step 2: Use and function of the phthalates in the medical device.
Objectives	Identify the full set of criteria to evaluate different alternatives. See Step 2: Use and function of the phthalates in the medical device; and Step 3: Assessment of the risks of the CMR/ED phthalate. See 7 Benefit assessment.
Alternatives	Identify alternatives that are being evaluated against each other. See Step 4: Inventory of possible alternatives; and Step 5: Identification of the candidates for assessment as potential relevant alternatives for phthalates.
Consequences	Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects in terms of the different benefits and risks. See Step 2: Use and function of the phthalates in the medical device; Step 3: Assessment of the risks of the CMR/ED phthalate; Step 6: Description of identified relevant potential alternative(s); Step 7: Assessment of the risk of identified potential relevant alternatives. For a summary table see Table 1. Example for a comparison of CMR/ED phthalate with potential alternative(s).
Trade-offs	Assess the balance between benefits and risks using judgements of weights associated with the criteria and the value associated with the benefits and risks of every alternative. MCDA techniques commonly achieve this through numerical analysis. A number of different weighting methods can be used. Conduct sensitivity analyses to explore uncertainties using different scenarios, and assess how different weights affect the overall ordering of the alternatives. See also 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 alternatives; Step 9: Comparison of risk(s) of original CMR/ED phthalate as used in the medical device with risk(s) of identified potential relevant alternatives; and Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified potential relevant alternatives.
Uncertainty	Report the uncertainty associated with the benefits and Risks. Consider how the balance between benefits and risks is affected by uncertainty. A quantitative model will

	explore in sensitivity analyses and scenario analyses (or by explicitly incorporating probability distributions in the model) the effects on the overall benefit-risk balance of all sources of uncertainty. See 1.9 Uncertainty analysis.
Risk tolerance	Describe any considerations that could or should affect the decision maker's attitude toward risks (e.g., special population, unmet medical need).
Linked-decisions	Discuss how the value judgements and data are consistent with similar decisions on medical devices.

References

- Dodgson J, Spackman M, Pearman A, Phillips LD. Multi-criteria analysis: A manual. London: Department for Communities and Local Government, First published in 2000 by the Department for Environment, Transport and the Regions; 2009.
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