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5 **Scientific Committee on Health, Environmental and 6 Emerging Risks**

7

SCHEER

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PRELIMINARY version of the

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Guidelines

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on the benefit-risk assessment of the presence of
12 phthalates in certain medical devices
13 covering phthalates which are carcinogenic, mutagenic, toxic to
14 reproduction (CMR) or have endocrine-disrupting (ED)
15 properties

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The SCHEER adopted this document by written procedure on 15 March 2019

22

1 **Abstract**

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

7
8 Phthalates are widely used in industry as plasticisers of polymers, in a variety of
9 applications such as coated fabrics and roofing membranes, as well as in medical
10 devices, adhesives, paints, inks and enteric-coated tablets. Di-(2-(ethylhexyl) phthalate
11 (DEHP) is the most widely used phthalate in medical devices. Dimethyl phthalate (DMP)
12 and diethyl phthalate (DEP) are not used as plasticisers but e.g. as additives in
13 cosmetics, medical devices, and household products.

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

17
18 The Medical Device Regulation, Regulation (EU) 2017/745 allows the use of CMR 1A/1B
19 and/or ED substances in medical devices above a concentration of 0.1% w/w. when a
20 proper justification can be provided (Annex I, Chapter II point 10.4). For such a
21 justification several steps need to be considered including the possible use of alternative
22 substances, materials, designs, and medical treatments. In addition, the risk in terms of
23 hazards associated with such alternatives should be weighed against the risk of the use
24 of CMR 1A/1B and/or ED identified phthalates covered under MDR Annex I Chapter II
25 point 10.4.1. However, the risk by itself is not the only parameter to consider: as also
26 the impact of the possible alternatives on the functionality, performance and the overall
27 benefit-risk ratio of the medical device shall be evaluated.

28
29 These Guidelines describe the methodology on how to perform a benefit-risk assessment
30 (BRA) for the justification of the presence of CMR 1A or 1B and/or ED phthalates
31 (CMR/ED phthalates) in medical devices and/or or parts or materials used therein at
32 percentages above 0.1% by weight (w/w).

33 They also consider the evaluation of possible alternatives for these phthalates used in
34 medical devices.

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

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

39
40 During the preparation of these Guidelines for BRA of the use of CMR/ED phthalates in
41 medical devices, SCHEER noticed that a number of BRA methodologies are theoretically
42 available. In addition, there is a considerable lack of data for potential alternatives to be
43 used in medical devices. Therefore, manufacturers are encouraged to produce
44 (semi)quantitative data on the use of alternatives for CMR/ED phthalates in medical
45 devices.

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

48
49
50 **Keywords:** Guidelines, benefit-risk assessment, CMR/ED phthalates, medical devices,
51 SCHEER

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

5 **Scope**

6 The Regulation (EU) 2017/745 on medical devices (MDR), Annex I "General Safety and
7 Performance Requirements", Chapter II "Requirements regarding design and
8 manufacture", point 10.4 deals with the presence of substances that may be released
9 from a medical device. Annex I Chapter II point 10.4.1 states that substances that are
10 carcinogenic, mutagenic, or reprotoxic (CMR) of category 1A and 1B, or substances
11 having endocrine-disrupting (ED) properties for which there is scientific evidence of
12 probable serious effects on humans, shall only be present in a device above 0.1% by
13 weight (w/w) when justified according to a set of criteria listed under point 10.4.2.

14 These Guidelines¹ describe the methodology on how to perform a benefit-risk assessment
15 (BRA) for the justification of the presence of CMR 1A or 1B and/or ED phthalates
16 (CMR/ED phthalates) in medical devices at percentages above 0.1% by weight (w/w).
17 They also consider the evaluation of possible alternatives for these phthalates used in
18 medical devices. They are intended to be used by the relevant stakeholders e.g.
19 manufacturers, notified bodies and regulatory bodies.

20 These Guidelines do not provide information for the BRA of the use of a medical device
21 itself. For the BRA of medical devices in general, elements of guidance are available in
22 section A7.2. of MEDDEV 2.7/1, revision 4. Additional information may be found
23 elsewhere, for example in the following documents FDA 2016, 2018, EN ISO 14971²,
24 ISO/TR 24971. It should be noted that the acceptability of any risk is evaluated in
25 relation to the benefit of the use of the medical device.

26 Annex 1 to these Guidelines describes the mandate, Annex 2 describes Annex I Chapter
27 II point 10.4. of the MDR regarding the use of hazardous substances, and Annex 3
28 describes the definitions used in these Guidelines.

29
30 **1. Introduction**
31

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

36
37

¹ It should be noted that, in accordance with EC 2017, Annex I, Chapter II points 10.4.3. and 10.4.4. (EC 2017, Annex I, Chapter II. Point 10.4.2), updates of these Guidelines might be available in the future.

² Annex ZA of EN ISO 14971 on the relationship of the standard with European legislation (EU Directive 93/42/EEC) contains deviations for which the content of EN ISO 14971 cannot be used to demonstrate compliance with the Directive.

1 For the purposes of this Regulation, the following definitions apply

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

6 — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of
7 disease,

8 — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or
9 disability,

10 — investigation, replacement or modification of the anatomy or of a physiological or
11 pathological process or state,

12 — providing information by means of *in vitro* examination of specimens derived from
13 the human body, including organ, blood and tissue donations, and which does not
14 achieve its principal intended action by pharmacological, immunological or metabolic
15 means, in or on the human body, but which may be assisted in its function by such
16 means.

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

18 — devices for the control or support of conception;

19 — products specifically intended for the cleaning, disinfection or sterilisation of
20 devices as referred to in Article 1(4) and of those referred to in the first paragraph of
21 this point.

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

30 For medical devices the horizontal standards EN ISO 14971 and EN ISO 10993-1 are
31 especially relevant. EN ISO 14971 describes the application of a risk management
32 process for medical devices, whereas EN ISO 10993-1 deals with the biological evaluation
33 and testing of medical devices within a risk management process. In EN ISO 10993-1, a
34 series of endpoints is indicated from which a selection can be made for the biological
35 evaluation of a medical device. The selection is based on the nature of the device's
36 contact with the body (device category: surface device, external communicating device,
37 or implant device; type of contact: skin, mucosal membrane, compromised surface,
38 blood, tissues, organs; duration of the contact: limited <24 h, prolonged >24 h to 30
39 days, permanent >30 days).

40 In addition to EN ISO 10993-1, a series of EN ISO 10993 standards has been published
41 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. 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). 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 device above 0.1% 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 with a presence 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 2016). 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) (10th ATP) 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).

SCENIHR adopted an Opinion on the safety of medical devices containing DEHP-plasticised PVC in 2008, and a revision of this Opinion in 2016 (SCENIHR 2008, 2016). 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 blood transfusions,

1 haemodialysis, and in neonatal intensive care units (NICU) for prematurely born
2 neonates (SCENIHR 2016). Although quite a number of alternative substances were
3 available for DEHP, serious data gaps were observed regarding hazard identification and
4 exposure estimation for some of them (Bui et al., 2016, SCENIHR 2016).

5 Phthalates classified as CMR of category 1A or 1B according to the procedure described in
6 Annex 4 are listed in Annex VI of the CLP regulation (CLP-Regulation (EC) No 1272/2008,
7 OJ L353). Phthalates can be identified as having ED-properties when there is scientific
8 evidence of probable serious effects to human health identified in the sense of article
9 57(f) of REACH (Regulation (EC) No. 1907/2006) or the Biocides Regulation (No.
10 528/2012).

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

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

18

19 **2. Framework for Benefit-Risk Assessment**

20

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

31 The justification for the presence of CMR 1A or 1B phthalates and/or ED phthalates for
32 which there is scientific evidence of probable serious effects on humans should be based
33 on a number of considerations as described below and in Figure 1.

34 In order to perform the BRA as indicated above, it is important to describe the
35 terminology to compare the risks of the presence of the phthalates to be evaluated (see
36 text box below). Annex 3 provides a selection of definitions as present in the MDR and/or
37 the OECD Substitution and Alternatives Assessment Toolbox
[\(http://www.oecdсааtoolbox.org/\)](http://www.oecdсааtoolbox.org/).

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

40

1 **“alternatives** are defined as substances, materials, designs and medical treatments that
2 can be used to replace the use of CMR and/or ED substances in medical devices”

3 The alternative therefore is not limited to a possible substitute substance or material but
4 could also be another device design (e.g. coating/production process/ techniques) or
5 medical treatment (e.g. procedure, device) or a combination of technical and substance
6 alternatives (modified from the ECHA REACH guidance on the preparation of an
7 application for authorisation).

8 The functionality and performance of the alternative shall be comparable to the extent
9 that there would be no clinically significant difference in the performance of the device or
10 in the outcome of the alternative medical procedure. Considerations of functionality and
11 performance shall be based on proper scientific justification. In order to justify the use of
12 a CMR 1A or 1B and/or ED phthalate, the manufacturer shall clearly demonstrate that the
13 identified alternative(s) are not appropriate to maintain the functionality, performance
14 and benefit-risk ratios of the medical device.

15 A number of aspects need to be considered for the justification of the presence of a
16 phthalate classified as CMR category 1A or 1B and/or identified as ED (i.e. content >
17 0.1% on w/w in a medical device.

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

21 Assessment of the used phthalate (use scenario)

22 Step 1:

23 Description and characterisation of the composition of the medical device.
24 Identification of the presence and concentration of CMR/ED phthalate.

25 Step 2:

26 Description of the use and function of the CMR/ED phthalate used in medical
27 device.
28 2a. Description of functionality/performance of the CMR/ED phthalate.
29 2b. Description of the benefit (material and/or clinical) of the presence of CMR/ED
30 phthalate in the medical device.

31

32 Step 3:

33 Assessment of the risks of the CMR/ED phthalate.
34 3a. Determination of the patient exposure based on realistic worst-case³ use
35 scenario in the intended use.
36 3b. Identification of biocompatibility, general toxicological and specific CMR/ED
37 hazards associated with the phthalate.

³ Realistic worst case is the situation where the exposure is estimated using from 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. The realistic worst case does not include deliberate misuse. (EU Biocides Regulation 528/2012).

- 1 3c. Determination of the maximum tolerable/acceptable exposure for the patient,
2 based on pre-clinical and clinical information (if available).
3 3d. Determination of the risks for various use scenarios and patient groups.

4

5 Assessment of possible alternatives (non-use scenario)

6 Step 4:

- 7 Inventory of possible alternatives.
8 4a. Substances.
9 4b. Materials.
10 4c. Designs and/or medical treatments⁴.

11

12 Step 5:

13 Identification of the candidates for assessment as potential alternatives for
14 phthalates and justification of the selection and/or exclusion of possible
15 alternatives.

16

17 Step 6:

- 18 Description of identified potential alternative(s).
19 6a. Description of functionality and performance of the potential alternative(s).
20 6b. Description of the benefit (material and/or clinical) of the use of the potential
21 alternative(s).

22

23 Step 7:

- 24 Assessment of the risk of identified potential alternatives.
25 7a. Determination of patient or user exposure of the alternative based on a
26 realistic worst-case use scenario in the intended use.
27 7b. Identification, where available, of biocompatibility, toxicological and CMR/ED
28 hazards associated with the alternative.
29 7c. Determination of maximum tolerable/acceptable exposure of the alternative
30 for patient (if available).
31 7d. Determination of risk of potential alternatives for various use scenarios and
32 patient groups.

33

34

35 Assessment of potential alternatives versus phthalate

36 Step 8:

37 Comparison of functionality and performance of CMR/ED phthalate as used in the
38 medical device with functionality and performance of identified potential
39 alternatives.

40

41

⁴ It should be noted that for alternative designs and/or medical treatments, appropriate endpoints for risks and benefits shall be selected.

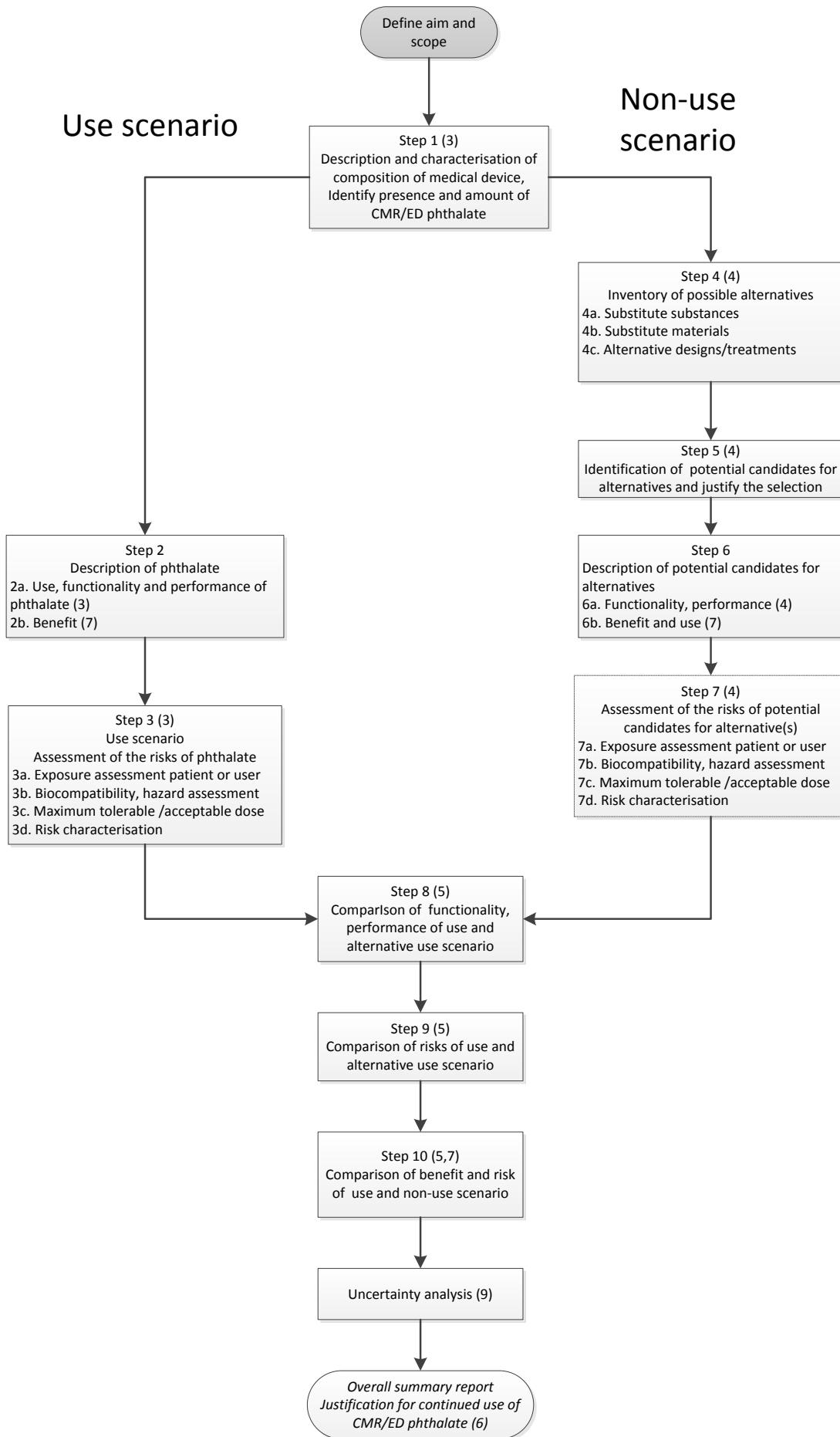
- 1 Step 9:
2 Comparison of risk(s) of original CMR/ED phthalate as used in the medical device
3 with risk(s) of identified potential alternatives.
4
5
- 6 Step 10:
7 Comparison of benefit and risk of CMR/ED phthalate used in the medical device
8 with identified potential alternatives.
9
- 10 Where appropriate, a similar approach shall be used for the justification of the presence
11 of CMR/ED phthalate in medical devices to evaluate the risk for professional users.
12 When alternative designs or medical treatments were identified as potential alternatives
13 in step 5, adequately adopted endpoints for risks and benefits shall be chosen.
14 It should be noted that scientific developments may be available in the future regarding
15 the use of alternatives for CMR/ED phthalates. Therefore, a revision of the BRA of the
16 presence of the CMR and/or ED phthalate may be necessary. Revisions of the above
17 indicated BRA shall occur as indicated in the relevant sections of MDR for the general risk
18 assessment of the medical device.
- 19 Figure 1 illustrates the BRA based on Eliason and Morose (2011), EMA (2014), FDA
20 (2016) and a critical selection from the OECD Substitution and Alternatives Assessment
21 Toolbox (<http://www.oecd-saatoolbox.org>). It presents the stepwise approach described
22 above including a general description of factors to consider when performing a BRA.

23

24

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

27



1 3. Assessment of the presence of phthalates in a medical device⁵

2

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

6 When more than one CMR/ED phthalate is used simultaneously in the medical device, a
7 justification shall be provided for each of the phthalates and their combination. Regarding
8 the combination of phthalates, EFSA has recently proposed a Group TDI for some of
9 them, having a similar Mode Of Action (MOA) (EFSA 2019, see Annex 5).

10
11 *Step 1: Description and characterisation of the composition of the medical device.*
12 Provide a description of the medical device and its composition including identification
13 and the concentration of each CMR/ED phthalate in the device. Use available chemical
14 information for identifying target phthalates (e.g. CAS N°; EINECS N°; IUPAC name).

15
16 *Step 2: Use and function of the phthalates in the medical device.*
17 Characterise the function and use of the CMR/ED phthalates in the medical device and
18 the properties it imparts to the device. Provide a description of the intended use,
19 functionality and performance of the medical device containing the CMR/ED phthalate.
20 For example, for PVC consider, with regard to the performance of the medical device,
21 maintenance, flexibility, durability and for the phthalate viscosity and PVC compatibility.
22 Provide a description of the patients targeted (e.g. with respect to sex, age, probable
23 vulnerable groups⁶). Provide a description of use types of the medical device for which it
24 is intended (e.g. single vs repeated exposure). ISO 10993-1 provides information on use
25 type in terms of exposure potential (e.g. limited (24h), prolonged (>24h to 30d) and
26 permanent (>30d)).

27
28 Benefits should also be considered. Present an inventory of the benefits of the CMR/ED
29 phthalates in the medical device for the patients (separately for vulnerable groups). More
30 detailed information on the benefit assessment is presented in section 7.

31
32 *Step 3: Assessment of the risks of the CMR/ED phthalate.*
33 Perform a risk assessment of the CMR/ED phthalate present in the medical device. The
34 risk assessment should contain a description of the potential phthalate exposure of
35 various patient groups for which the medical device is intended (e.g. single vs repeated
36 exposure). This should separately include the vulnerable groups.

37

⁵ 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.

⁶ 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.

- 1 Provide information, preferably based on data from direct measurement or, when not
2 available, an estimation based on worst-case scenario or from scientific literature, on the
3 release of the CMR/ED phthalate from the medical device when used in various clinical
4 modalities. For data generation, analytical contact conditions for the evaluation of
5 leaching of substances from medical devices, should consider for example temperature,
6 contact duration and frequency, polarity of contact liquids, flow rates, contact surface,
7 and volume of contact liquids. The contact conditions should be set to represent realistic
8 worst-case conditions taking into account the intended use of the medical device.
9
- 10 Estimate exposure to the phthalate(s) considering data on the release of the substance
11 from the device. Consider multiple use scenarios (e.g. frequent use of a dialyzer, various
12 types of possible contact) and different population groups. The combined exposure to
13 multiple phthalates shall also be considered when present in medical devices. More
14 details are presented in Annex 6. In addition, data from biomonitoring programs may
15 become available that could also provide information on exposure levels of phthalates.
16
- 17 Describe hazards associated with the CMR/ED phthalate by considering all relevant
18 toxicological endpoints for acute as well as for repeated dose toxicity. Possible
19 hazardous effects of combined exposure should also be assessed. Identify an adequate
20 point of departure (PoD) for risk assessment. In case of a threshold Mode of Action, such
21 a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-
22 observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response
23 (Benchmark dose – BMD) obtained by Benchmark dose modelling. In case of non-
24 threshold effects (e.g. in the case of genotoxic carcinogens or for substances acting via
25 an ED-mediated MoA), such a dose descriptor could be a T25 value or the benchmark
26 dose associated with a 10% response (BMD10) (ECHA, 2012).
27 Where a DNEL and/or a DMEL have already been derived in the context of other EU
28 legislations, the analysis could refer to these derived figures without referring to detailed
29 assessment how these data have been derived (e.g. under REACH legislation, Food
30 Contact Material legislation). Some of these other legislations are defined under Annex 4.
31 In addition, information can also be obtained in the SCENIHR 2016 Opinion on DEHP.
32
- 33 The ED property of the phthalate can be described according to the recently published
34 EFSA/ECHA guidance document
35 (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf). This includes impacts
36 on fertility, birth defects (e.g., cryptorchidism, hypospadias), developmental effects, and
37 other effects associated with the CMR/ED phthalates.
38
- 39 Describe risk (risk characterisation)
40
- 41 The risk can be described by comparing exposure levels that are considered safe with the
42 expected exposure (worst-case scenario) to obtain a risk characterisation ratio (RCR).
43 Exposure levels that are considered safe could be a "Derived No-Effect Level" (DNEL) for
44 threshold substances, a "Derived Minimum Effect Level" (DMEL) for non-threshold
45 substances or intakes over lifetime without presenting an appreciable risk to health (ADI
46 or TWI). When necessary, they can be derived by dividing the point of departure for risk
47 assessment by appropriate assessment or uncertainty factors.
48

- 1 The risks can also be described by calculation of the Margin of Safety (MoS), which is the
2 ratio between the lowest PoD and the expected exposure (worst case scenario) and
3 comparison with a reference MoS (see SCCS Notes of Guidance – SCCS/1602/18).
4
- 5 Determine and describe in which situation the risk can be acceptable for the use of the
6 CMR/ED phthalate in the medical device. Describe risk control measures in place (EN ISO
7 14971) and monitoring programs, if applicable. The MDR considers a risk acceptable
8 when outweighed by the benefit of using the device in patients (Chapter I of MDR).
9
- 10 In addition to potential CMR/ED effects, discuss any other potential hazards associated
11 with the composition of the device. Evaluate if such effects are associated with the use of
12 the CMR/ED phthalates in the device.
13
- 14 Note: It should be realised that for some genotoxic carcinogens a no effect level does not
15 exist. Similarly, a scientific debate is ongoing about whether this also applies to ED
16 activity.
17
- 18 The assessment of the risk should be accompanied by an estimation of the impact of
19 uncertainties in the described outcomes (see section 9).
20
21

22 **4. Assessment of possible alternative substances, materials, designs or**
23 **medical treatments⁷**

- 25 In general a similar risk assessment as presented in step 3 above has to be performed
26 for the alternative (substances, materials, designs or medical treatment) that would
27 replace the CMR/ED phthalate. An inventory should be prepared in order to be able to
28 evaluate possible alternatives. An alternative could be another substance/material or
29 device design modification or it could be a clinical procedure (e.g. a process, technique,
30 treatment or modification) or a combination of technical and substance alternatives.
31 Instead of using PVC with a phthalate as plasticiser, or replacing the phthalate also other
32 materials such as natural or synthetic polymers can be used. The application of
33 biodegradable polymers is of increasing importance for implantable medical devices.
34 Typical representatives of such biodegradable polymers are poly-L-lactide (PLA),
35 polyglycolic acid (PGA), polyhydroxybutyrate (PHB) and polycaprolactone (PCL).

- 36
37
- 38 *Step 4: Inventory of possible alternatives*
39 Prepare a list of possible alternatives (including substances, materials, designs or medical
40 treatments).
- 41 A description of the alternative scenario (CMR/ED phthalate "non-use scenario") needs to
42 be presented including identification of alternative substances, materials, designs or
43 medical treatment, e.g. by including consideration of all available information, such as

⁷ 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.

1 alternative medical devices available on the market, information about independent
2 research, published peer-reviewed studies, systematic literature reviews, risk assessment
3 reports or scientific opinions from relevant scientific committees and the results of in-
4 house research and development. The identification of possible alternatives should be
5 properly documented.

6

7 *Step 5: Identification of the candidates for assessment as potential alternatives for*
8 *phthalates*

9 The MDR indicates that an analysis of all possible alternatives shall be performed.
10 However, when many alternatives are available it would not be feasible to do an
11 extensive evaluation of all alternatives. It is therefore recommended to select a number
12 of potential alternatives. This choice might be influenced by data on functionality as well
13 as performance and/or toxicity (see below).

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

20

21 Information/data on functionality (e.g. level of flexibility in tubes) as well as performance
22 and/or chemical safety assessment (e.g. hazard profile) may be used for rejection of the
23 less likely alternatives (see below).

24

25 Finally, a short list of the potential alternatives can be chosen for further detailed
26 assessment with regard to technical feasibility, health benefits, comparison of risks,
27 existing legal requirements, economic feasibility, availability (e.g. sufficient availability or
28 accessible to the applicant), and technical performance.

29

30 A compilation of resources and elements in support of chemical substitution and an
31 assessment of alternatives can be found on the OECD webpage:
32 <http://www.oecd-saatoobox.org/>

33

34 *Step 6: Description of identified potential alternative(s)*

35 CMR/ED phthalates are present in medical devices for a specific purpose depending on
36 the intended use of the medical device. For example, phthalates offer the possibility for
37 fine tuning the flexibility of a PVC-based medical device. In addition, DEHP has a
38 stabilising effect on red blood cells in blood bags (SCENIHR 2016). Therefore, the
39 assessment of the functional properties in relation to the intended use of the medical
40 device is essential. Besides functionality, performance under intended use conditions
41 should also be considered. Based on the outcome of the functionality evaluation, the
42 choice of the potential candidates might be reconsidered and some might be discarded
43 before performing the risk assessment (see Step 7).

- 1 Argumentation shall be provided for justifying why possible substances and/or material
2 substitutes, if available, or design or medical treatment changes, if feasible, are
3 appropriate or inappropriate in relation to maintaining the functionality and/or
4 performance of the medical device. For example, it might be the case that replacement is
5 possible for one specific functional use whereas for another functionality the use of the
6 CMR/ED phthalate remains necessary.
- 7 The benefit(s) should also be considered. An inventory of the benefit(s) of the potential
8 alternative substances, materials, designs or medical treatments for patient populations
9 (separately for vulnerable patient groups) should be presented (see section 7).

10

11

12

13 *Step 7: Assessment of the risk of identified potential alternatives*

14 The risk assessment of alternatives is comparative in nature. Its aim is to assist in the
15 conclusion in section 5 whether the transition to the alternatives would lead to lower risk
16 to human health for patients when compared to the current use of the CMR/ED
17 phthalates in the medical device. This step is similar to step 3 as performed for the
18 phthalate to be replaced by the alternative.

19

20 A risk assessment of the potential alternative substance/material used in the medical
21 device or designs or medical treatments should be performed. The risk assessment
22 should contain a description of the potential substance/material (alternative medical
23 procedure) exposure of various patient groups for which the medical device is intended to
24 be used (considering single or repeated use). This should include separately vulnerable
25 groups.

26

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

32

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

44

45 For the hazard identification special attention should be on the determination of any
46 potential CMR and/or ED property of the alternative substance used. This is of special
47 importance as the substance will replace an already known CMR/ED phthalate. For
48 further information purposes, a procedure is described in ECHA Guidance on the

1 application of the CLP criteria
2 (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-
3 [9702-e9e1f5051cc5](#)) or by searching Annex VI of CLP regulation. ED properties of the
4 alternative substance/material can be described according to the recently published
5 EFSA/ECHA guidance document
6 (https://echa.europa.eu/documents/10162/23036412/bpr_guidance_identif_ed_en.pdf/1
7 [a4d2811-3faa-fe61-1de2-3cbce8fd4d95](#)). These effects include impacts on fertility, birth
8 defects (e.g., cryptorchidism, hypospadias), developmental effects, and other potential
9 toxic effects associated with phthalates with ED properties and reprotoxic effects
10 category 1A/B. It needs also to be considered that the potential alternative (substances,
11 materials, designs or medical treatments) would also have other hazards than those of
12 the CMR/ED activity. These other hazards should be discussed.

13
14 Description of risk (risk characterisation)

15 The risk can be described by comparing exposure levels that are considered safe with
16 the expected exposure (realistic worst case use scenario). Exposure levels that are
17 considered safe could be "Derived No Effect-Levels" (DNELs) for threshold substances,
18 "Derived Minimum Effect Levels" (DMELs) for non-threshold substances or intakes over
19 lifetime without presenting an appreciable risk to health (ADI or TWI). They can be
20 derived by dividing the point of departure for risk assessment by appropriate assessment
21 or uncertainty factors.

22
23 The risks can also be described by calculation of the Margin of Exposure (MoE) or the
24 Margin of Safety (MoS), which is the ratio between the lowest PoD and the expected
25 exposure realistic worst case use scenario) and comparison with a reference MoS (see
26 SCCS Notes of Guidance – SCCS/1602/18).

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

29
30 Where a DNEL and/or a DMEL have already been derived in the context of other EU
31 legislations, the assessment could refer to these derived figures without referring to a
32 detailed assessment of how these data have been derived (e.g. under REACH legislation,
33 Food Contact Material legislation). The risk can also be described by the so-called risk
34 characterisation ratio (RCR), being a ratio between the exposure and the DNEL.

35
36 Determine and describe acceptability of the risk for the use of the potential alternatives.
37 Risks may be acceptable when they are outweighed by the benefits for the patient.
38 Describe risk control measures in place (EN ISO 14971) and monitoring programmes, if
39 applicable.

40
41 Consider any known adverse events associated with the operation of the device using the
42 phthalate, and whether the potential alternatives might affect these adverse events.
43 These considerations can be based upon a systematic literature review.

44
45 This exercise has to be performed for each possible alternative substance and/or
46 materials identified as a likely replacement for the CMR/ED designated phthalate.

47
48 A large number of phthalates exist and some may be substitutes for the CMR/ED
49 phthalate currently used in the medical device. However, a number of these phthalates

1 are also classified as CMR and/or designated ED (see above and Table 1 Annex 5). Such
2 phthalates might be used as alternatives when the CMR/ED risk is reduced compared to
3 the intended phthalate to be used. In addition, different substances, have also been
4 proposed as alternative plasticisers. In 2016 SCENIHR published an updated Opinion of
5 potential alternative plasticisers for DEHP (SCENIHR 2016). Although many alternatives
6 were potentially available, it was also observed that for many of them the information on
7 potential risks and the necessary risk assessment was rather limited precluding their use
8 as alternatives. For DEHP an extensive amount of literature is available, allowing a very
9 careful evaluation of the risk associated to its use.

10 Note shall be taken that alternative designs or medical treatments might lead to
11 adaptation of endpoints for the benefit-risk assessment.

12 The assessment of the risk should be accompanied by an estimation of the uncertainties
13 in the described outcomes (e.g. confidence interval, standard deviation).

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

20 **5. Assessment of potential alternative substances, materials, designs or** 21 **medical treatments versus phthalates**

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

29 *Step 8: Comparison of functionality and performance of CMR/ED phthalate as used in the*
30 *medical device with functionality and performance of identified potential alternatives.*

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

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

35 If several alternatives have a similar functionality and hazard profile, exposure conditions
36 and possibilities for Risk Management Measures (RMM) resulting in risk reduction should
37 be considered (see below).

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

3
4 Compare the risk of both CMR/ED phthalate and alternative substance/material (or
5 designs or medical treatments by choosing adequate endpoints).

6 Perform step 9 for each potential alternative.

7

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

23
24
25 *Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device
26 with identified potential alternatives.*

27
28 Present summary/overview of comparison of benefit and risk of CMR/ED phthalate used
29 in the medical device with the potential alternatives, including uncertainties about the
30 estimates or reliability of the data, assumptions, etc. for the parameters presented. The
31 summary should contain various aspects of functionality, performance, risk and benefit of
32 the use of the original CMR/ED phthalate used in the medical device and the most likely
33 alternative. See section 6 below in which the justification of the use of a CMR/ED
34 phthalate is described based on the summary table comparing an alternative with the
35 CMR/ED phthalate.

36 Perform step 10 for every potential alternative.

37
38 Each of the assessments performed in steps 1 to 10 is associated with uncertainties.
39 Certain uncertainties can be described by the use of measures like the standard deviation
40 or confidence interval. For other uncertainties, a description may be necessary to explain
41 the extent of the uncertainty and its impact on the final outcome.

42
43 Benefit and risks should be described and weighted against each other in the use of the
44 potential alternative substance/material in the medical device (or designs or medical
45 treatments by choosing adequate endpoints) similar to the procedure for the CMR/ED
46 designated phthalate (see step 2).

47

1 6. Justification for the use of CMR/ED phthalate

2

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

9
10 Explain the importance of any difference in terms of benefits and risks between the
11 CMR/ED phthalate to be used in the medical device and potential alternatives using value
12 judgements and explain how the use of the CMR/ED phthalate can be justified over the
13 alternatives by describing the acceptability of trade-offs in the achievement of some
14 performance criteria against others. Any advantage in benefits needs to be weighed
15 against possible disadvantages in terms of functionality and risks. Both differences in
16 benefits and risks need to be considered jointly.

17
18 In building the argumentation for the use of a CMR/ED phthalate, note can be taken of
19 the Memorandum on weight of evidence and uncertainties of SCHEER (SCHEER 2018).
20 This Memorandum describes a methodology that classifies the strength of evidence in the
21 human health risk assessment based on integration of different lines of evidence into
22 strong, moderate, weak, uncertain and inconclusive (no suitable evidence available).

23
24 The argumentation should specifically take into account the intended use of such devices.
25 This should include consideration and discussion of possible high risk groups such as
26 children or pregnant or breastfeeding women, and other patient groups considered
27 particularly vulnerable to such substances and/or materials. In addition, where applicable
28 and available, any future update of these Guidelines shall be considered. A Table with the
29 most relevant information and values should be used to present an overview of the
30 performed assessment comparing the CMR/ED phthalate with potential alternative(s). An
31 non-exhaustive example of such Table is presented below. The Table can be extended
32 depending on the number of criteria evaluated and the number of potential alternatives
33 identified.

34
35 **Table 1:** Example for a comparison of CMR/ED phthalate with potential alternative(s).

Assessment criteria	Description (examples)	Reference phthalate	Alternative I	Alternative II etc.
Functionality/performance	Used as plasticiser	e.g. DEHP		
Clinical benefit/performance	Treatment possibility	e.g. Flexibility of tubing / red blood cells storage		
Concentration (% w/w)				
Leaching from medical device (mg per hour/day)				
Exposure estimation				

(realistic worst case use scenario)				
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)				
Risk characterisation (MoE, MoS, RCR)				
Confidence estimation (see Table 2)				
Feasibility				
Other				

1

2 This Table shall be completed for every component of the medical device that contains
 3 CMR/ED phthalate(s). Note that in case of alternative designs or medical treatments
 4 adequate endpoints for the comparison shall be chosen. These endpoints may represent
 5 risks that may be of a different nature than that of the risk of the phthalate.

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

12 A balanced weighing of the benefit-risk ratio has to be performed. For example it is
 13 possible to use a combination of a CMR/ED phthalate and PVC/material with high intrinsic
 14 toxicological hazards, thus accepting a risk from a toxicological perspective, in case the
 15 clinical benefit exceeds the risk. In contrast, a slight clinically insignificant loss in
 16 functionality might be acceptable if there is a large benefit to be gained in terms of
 17 reduced or even absence of toxicity. Each comparison of a potential alternative for the
 18 use of a phthalate should be based on the combination of functionality, risk and benefits
 19 for patients.

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

8 Although not the main subject of these Guidelines, it should be realised that availability
9 might be a limitation for the introduction of an alternative substance/material. The lack
10 of the availability of a potential alternative for a medical device might result in the
11 conclusion that replacement is not feasible and that the use of a phthalate with CMR
12 and/or ED property continues in order to keep the availability of the device for patients.
13 So, besides technical feasibility in terms of functionality and risk reduction (risk
14 assessment of the phthalate versus the alternative), also availability needs to be
15 considered.

16

17 **7. Benefit assessment**

18
19 These Guidelines do not provide information for the benefit-risk assessment of the use of
20 a medical device itself but are limited to the evaluation of potential alternatives to the
21 use of CMR 1A or 1B and/or ED phthalates in a medical device.

22

23 **7.1 Material benefit**

24

25 A medical device does not achieve its principal intended action by pharmacological,
26 immunological or metabolic means, in or on the human body, but may be assisted in its
27 function by such means. For the use of phthalates in medical devices, additional
28 functionalities need to be considered. One of the functionalities is the fine-tuning of the
29 flexibility of PVC when used as plasticisers e.g. in intubation devices. In addition, some
30 phthalates (e.g. DEHP) may have an additional function such as the stabilising effect on
31 red blood cells (RBCs) (SCENIHR 2016). For blood bag materials other requirements are,
32 for example, resistance to heat and chemicals, especially during sterilisation, and
33 permeability of gases to assure that pH and oxygen levels remain stable. Butyryl-tri-n-
34 hexylcitrate (BTHC) was developed for RBC containers with a storage capability at 40°C
35 up to 35 days (Simmchen et al., 2012).

36 Platelets are extremely sensitive to changes in the pH of the medium in which they are
37 suspended, so sufficient gas permeability to O₂ and CO₂ has to be assured in the
38 containers devoted to their storage (Simmchen et al., 2012). For this reason, DEHP has
39 been almost fully replaced with Tri(2-ethyl hexyl)trimellitate (TEHTM) because a better
40 gas exchange has been found in bags plasticised with TEHTM. This allows the storage of
41 platelet concentrates for up to 7 days, if measures to prevent bacterial contamination can
42 be safely implemented.

1 It should be realised that the benefit of phthalates in terms of material functionality and
2 performance may differ from device to device. The use of an alternative may be possible
3 for one application while this may not be possible for another in view of added or specific
4 demands on the functionality of the phthalate.

5

6 **7.2 Clinical benefits**

7

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

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

13 This "clinical benefit" has to be substantiated by the manufacturers in the "clinical
14 evaluation" of the medical device, which includes a number of considerations. This
15 includes a discussion and overall conclusions covering safety and performance results,
16 assessment of risks and clinical benefits, discussion of clinical relevance in accordance
17 with clinical state of the art, any specific precautions for specific patient populations,
18 implications for the investigational device and limitations of the investigation.

19 A 'clinical benefit' could include any meaningful, measurable, patient-relevant outcome as
20 presented below. Examples that may be relevant for the use of phthalates include (list
21 not exclusive):

- 22 • Improved survival rates
- 23 • Improved length of hospital stay
- 24 • Improved time of intervention
- 25 • Improved time of placing (among others in tubes and catheters)
- 26 • Improved clinical performance (among others in tubes and catheters) in terms of:
 - 27 ◦ Improved leakage rates
 - 28 ◦ Improved breakage rates
 - 29 ◦ Improved knotting rates
 - 30 ◦ Improved blockage rates
 - 31 ◦ Improved bending performance rates
 - 32 ◦ Improved release rates of toxic substances
 - 33 ◦ Improved release rates of (nano-)particles
- 34 • Improved displacement rates
- 35 • Improved possibilities for sterilisation
- 36 • Reduction of diameters in relation to performance
- 37 • Possibility to produce "multiple-purpose" devices, (e.g. inclusion of additional
38 sensors), and therefore reduction of over-all patient-stress and patient-impact
- 39 • Improved observability (safety) in terms of translucence, printability, radiopaque
40 lines included, identifiability, traceability, etc. (among others in tubes and
41 catheters)
- 42 • Fewer adverse events, e.g. reduced mucosal or endothelial irritation or injury
43 rates (among others in tubes and catheters)
- 44 • Fewer serious adverse events

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

5

6

7 **8. Methodologies for Benefit –Risk Assessment**

9 In general, a Benefit - Risk Assessment (BRA) aims to evaluate the desired effects of
10 therapeutic means, medicines or devices, against their undesired effects, i.e., risks for
11 human health. An appropriate BRA can contribute to a more objective analysis and help
12 authorities towards a more objective and transparent decision-making process. Weighing
13 the benefits and risks can be a complex task. It may involve the evaluation of a large
14 amount of data that should be as accurate as possible, without methodological
15 weaknesses and biases. There is always some uncertainty around the actual benefits and
16 risks, because they can only be determined by looking at the information that is available
17 at a given point in time that may include various sources of uncertainty.

18 For the BRA of medical devices in general, elements of guidance are available in section
19 A7.2. of MEDDEV 2.7/1, revision 4. Additional information may be found elsewhere, for
20 example in the following documents FDA 2016, 2018, EN ISO 14971, ISO/TR 24971. It
21 should be noted that the acceptability of any risk is evaluated in relation to the benefit of
22 the use of the medical device.

23 Several methodologies for such a BRA have been proposed (Guo et al, 2010, Mt-Isa et al.
24 2014), of which most methodologies are so far mainly used for pharmaceutical products.
25 However, it should be underlined that for medical devices the quantitative determination
26 of a benefit-risk ratio may be rather difficult to provide. One methodology, namely the
27 multi criteria decision analysis (MCDA), can be generally applied to various areas of BRA.
28 Therefore, this methodology might also be suitable for performing the BRA of medical
29 devices (see Annex 7). The MCDA methodology has its origins in decision theory aiming
30 to evaluate multiple conflicting criteria in decision making. These criteria can include the
31 benefits and risks of the use of a medical device on human health.

32 The final BRA of both the used CMR/ED phthalate and potential alternatives should
33 contain all aspects as indicated in the framework above. It is well known for medical
34 devices that not all aspects can be expressed quantitatively and that qualitative
35 information can also have an important role in this benefits to risks comparison.

36 A quantitative or semi-quantitative description of the risks (e.g. MoS, RCR) and of the
37 benefits of a medical device containing a CMR/ED phthalate or alternative should be the
38 basis for a BRA if possible. Although quantitative approaches to the BRA are preferable, a
39 qualitative description of the value judgements about the balance of benefits and risks
40 might also be an appropriate approach when justified (see step 10).

41

1 **9. Uncertainty analysis**

2

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

9 There are various sources of uncertainty in bio-medical studies; a major source of
10 uncertainty is the biological differences among individuals. Another source of uncertainty
11 is the intra- and inter- variability of the laboratories, with respect to equipment,
12 reagents, and methods used. It is also accepted that diagnostic tools which evaluate
13 benefit and risk share several boundaries, giving false negative and false positive results
14 in a variety of cases. Observer variation occurs quite often and should always be taken
15 into account. Other factors that may influence the degree of uncertainty include: the type
16 of clinical information available (e.g., clinical trial data, observational studies, evidence
17 derived from registries or commercial experience), the representativeness of the
18 information (e.g., sample size, relevance of the sample to the referent population
19 exposed to the device), as well as the statistical inferences derived from the information.

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

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

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

40 EFSA: Main elements of uncertainty analysis

- 41 • Identifying uncertainties affecting the assessment. This is necessary in every
42 assessment and should be done in a structured way to minimise the chance of
43 overlooking relevant uncertainties. In assessments that follow standardised
44 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 no non-standard uncertainties are identified.
- 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 no non-standard uncertainties are identified.

A number of methods that can be used in the uncertainty analysis are presented below.

- 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.

- 1 After performing the uncertainty analysis, the observed overall confidence associated
2 with a BRA can be expressed in a kind of probability score. This score gives the risk
3 assessor an indication what the uncertainty is in the BRA.
- 4 In situations where sufficient data are available, a quantitative categorisation of
5 probability levels is preferred. If this is not possible, the manufacturer should give a
6 qualitative description. A good qualitative description is preferable to an inaccurate
7 quantitative description (EN ISO 14971).
- 8 EFSA (EFSA, 2018b) and SCHEER (2018) use a rather detailed probability scale of 9 and
9 7 probability levels, respectively. EFSA stresses that this scale may be used as an aid to
10 support the development of judgements and that other ranges or qualitative descriptions
11 can be used as well. EFSA (2018b) also argues that presenting the numerical
12 probabilities alongside verbal expressions of probability, e.g. 'Likely (> 66% probability)',
13 increases the consistency of interpretation.
- 14 A detailed scale does not seem to be applicable for the certainties that can be obtained
15 during a BRA evaluation of medical devices. For medical devices, a probability scale as
16 indicated in Table 2 may be used EN ISO showing a 5-level scale recommended by ISO
17 for semi-quantitative assessments (EN ISO 14971, Table D4). Table 2 further shows the
18 verbal terms and subjective probability ranges that are based on a simplification of the
19 EFSA/SCHEER scales.

20

21 **Table 2: Probability scale for (semi-)quantitative description of the overall
22 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

23

24

1 **10. Conclusions**

2

3 These Guidelines are intended to be used for a BRA of the presence of phthalates in
4 certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to
5 reproduction (CMR) or have endocrine-disrupting (ED) properties. The Guidelines can be
6 used for the justification of the use of CMR/ED phthalates in a medical device according
7 to the Regulation (EU) 2017/745 on medical devices. It also provides a framework on
8 how to assess and compare possible alternative substances, materials, designs or
9 medical treatments to the use of CMR/ED phthalates in medical devices. Major aspects
10 include the functionality of phthalates, the performance of the medical device with the
11 phthalate or the potential alternative for the phthalate, as well as the risk assessment of
12 the phthalate or alternative used. In the end, the benefit(s) shall be weighted against the
13 possible risk of the use of the CMR/ED phthalate and the alternative substance,
14 materials, designs or medical treatments. This overall analysis will determine whether it
15 is justified or not to use a CMR/ED phthalate in a medical device.

16 During the preparation of these Guidelines for BRA of the use of CMR/ED phthalates in
17 medical devices, SCHEER noticed that a number of BRA methodologies are theoretically
18 available. In addition, there is a considerable lack of data for potential alternatives to be
19 used in medical devices. Therefore, manufacturers are encouraged to produce
20 quantitative data on the use of alternatives for CMR/ED phthalates in medical devices.

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

23

24

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- 30
- 31
- 32

1 **C. ANNEXES**

2

3 **Annex1: SCHEER mandate on benefit risk assessment on the use of CMR/ED phthalates**

4

5

6 **1. Background**

7

8 **What are phthalates?**

9 Phthalates are the esters of 1,2-benzenedicarboxylic acid (o-phthalic acid) and their
10 chemical structure consists of one benzene ring and two ester functional groups linked
11 with two consecutive carbons on the ring⁸. The hydrocarbon chains of the ester groups
12 are either straight or branching; they give each substance its name and they are
13 responsible for the different properties among phthalates. Phthalate esters (PEs) may be
14 categorised into three distinct groups according to the length of their carbon chain. High
15 molecular weight (HMW) phthalates include those with 7–13 carbon atoms in their carbon
16 chain and low molecular weight (LMW) those with 3–6 carbon atoms in their backbone.
17 DEHP is classified as a LMW phthalate. A third group includes dimethyl phthalate (DMP)
18 and diethyl phthalate (DEP)⁹.

19

20 **What are they used for?**

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

27

28 **Potential CMR or endocrine-disrupting properties**

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

32 Correlation between exposure to a range of phthalates and adverse health effects has
33 been documented in animals and humans (see for example tables in Mariana *et al.* 2016

⁸ 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>

⁹ 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.

1 and Katsikantami *et al.* 2016). A number of phthalates are suspected of and/or have
2 been classified or identified as having CMR or endocrine-disrupting properties.

3

4 **Previous work of Commission Scientific Committees on phthalates**

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

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

22

23 **The legal obligation**

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

27 Accordingly, Section 10.4 of Annex I, which deals with substances in medical devices,
28 states that "*Devices shall be designed and manufactured in such a way as to reduce as*
29 *far as possible the risks posed by substances or particles, including wear debris,*
30 *degradation products and processing residues, that may be released from the device.*"
31 Particular substances of concern are those which (a) are carcinogenic, mutagenic or toxic
32 to reproduction (CMR), of category 1A or 1B,¹⁰ or (b) have endocrine-disrupting
33 properties (ED)¹¹. The Regulation states that:

34

35 "*Devices, or those parts thereof or those materials used therein that:*

36 *– are invasive and come into direct contact with the human body,*

¹⁰ in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008

¹¹ identified as such in accordance with the relevant provisions of Regulation (EC) No 1907/2006 or respectively of Regulation (EU) No 528/2012

- 1 – *(re)administer medicines, body liquids or other substances, including gases,
2 to/from the body, or
3 – transport or store such medicines, body fluids or substances, including gases, to
4 be (re)administered to the body"*

5

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

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

15

16 **2. Terms of reference**

17

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

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

- 25 • are invasive and come into direct contact with the human body,
26 • (re)administer medicines, body liquids or other substances, including gases,
27 to/from the body, or
28 • transport or store such medicines, body fluids or substances, including gases, to
29 be (re)administered to the body.

30

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

- 32 • analyse and estimate potential patient or user exposure to the substance,
33 • analyse possible alternative substances, materials, designs, or medical
34 treatments,
35 • to justify why possible substance and/or material substitutes, if available, or
36 design changes, if feasible, are inappropriate in relation to maintaining the
37 functionality, performance and the benefit-risk ratios of the product, including
38 taking into account if the intended use of such devices includes treatment of
39 children or treatment of pregnant or breastfeeding women or treatment of other
40 patient groups considered particularly vulnerable to such substances and/or
41 materials.

42

43 In addition, the Scientific Committee is requested to:

Guidelines on the benefit-risk assessment of the presence of CMR/ED phthalates in certain medical devices (Preliminary version)

- 1 • identify any relevant knowledge gap; and
2 • to give consideration to what extent of new evidence would be deemed
3 appropriate to justify an update of these guidelines before the maximum period of
4 five years.
5

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

- 8 • involve at the appropriate level the notified bodies active in the field of medical
9 devices, or other relevant stakeholders such as Competent Authorities,
10 professional and patient associations, industry associations, while maintaining
11 scientific independence;
12 • involve to the necessary extent the relevant EU Agencies and Scientific
13 Committees;
14

1 **Annex2:** Medical Device Regulation (Regulation 2017/745) on CMR and/or ED
2 substances

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

6
7
8 10.4. Substances

9
10 10.4.1. Design and manufacture of devices

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

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

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

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

22 (a) substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category
23 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the
24 European Parliament and of the Council (1), or

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

32 10.4.2. Justification regarding the presence of CMR and/or endocrine-disrupting substances

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

- 34 (a) an analysis and estimation of potential patient or user exposure to the substance;
35 (b) an analysis of possible alternative substances, materials or designs, including, where
36 available, information about independent research, peer-reviewed studies, scientific opinions
37 from relevant scientific committees and an analysis of the availability of such alternatives;
38 (c) argumentation as to why possible substance and/ or material substitutes, if available, or
39 design changes, if feasible, are inappropriate in relation to maintaining the functionality,
40 performance and the benefit-risk ratios of the product; including taking into account if the
41 intended use of such devices includes treatment of children or treatment of pregnant or
42 breastfeeding women or treatment of other patient groups considered particularly vulnerable to
43 such substances and/or materials; and
44 (d) where applicable and available, the latest relevant scientific committee guidelines in
45 accordance with Sections 10.4.3 and 10.4.4.

1 **Annex 3: Definitions/descriptions – References - Glossary**
2

3 ***Definitions (Regulation (EU) 2017/745)***
4

5 **Benefit-risk determination:** means the analysis of all assessments of benefit and risk
6 of possible relevance for the use of the device for the intended purpose, when used in
7 accordance with the intended purpose given by the manufacturer.
8

9 **Performance:** means the ability of a device to achieve its intended purpose as stated by
10 the manufacturer.
11

12 **Clinical performance:** means the ability of a device, resulting from any direct or
13 indirect medical effects which stem from its technical or functional characteristics,
14 including diagnostic characteristics, to achieve its intended purpose as claimed by the
15 manufacturer, thereby leading to a clinical benefit for patients, when used as intended by
16 the manufacturer.
17

18 **Clinical benefit:** means the positive impact of a device on the health of an individual,
19 expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s),
20 including outcome(s) related to diagnosis, or a positive impact on patient management or
21 public health.
22

23 **Risk:** means the combination of the probability of occurrence of harm and the severity of
24 that harm.
25

26 **Adverse event:** means any untoward medical occurrence, unintended disease or injury
27 or any untoward clinical signs, including an abnormal laboratory finding, in subjects,
28 users or other persons, in the context of a clinical investigation, whether or not related to
29 the investigational device.
30

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

1

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

6

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

11

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

16

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

20

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

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

28

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

34

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

38

1 **Clinical:** the device is used for the same clinical condition or purpose, including similar
2 severity and stage of disease, at the same site in the body, in a similar population,
3 including as regards age, anatomy and physiology; has the same kind of user; has
4 similar relevant critical performance in view of the expected clinical effect for a specific
5 intended purpose. The characteristics shall be similar to the extent that there would be
6 no clinically significant difference in the safety and clinical performance of the device.
7 Considerations of equivalence shall be based on proper scientific justification. It shall be
8 clearly demonstrated that manufacturers have sufficient levels of access to the data
9 relating to devices with which they are claiming equivalence in order to justify their
10 claims of equivalence.

11

12

13 **Definitions on assessment of alternatives (OECD Toolbox Glossary)**

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

15

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

19

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

23

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

28

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

34

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

38

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

2

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

7

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

11

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

14

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

18

19 ¹ Adapted from *Alternatives Assessment Guide, version 1.0*. 2013. Interstate Chemicals
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25 Recommendation to the EPA Administrator and Deputy Administrator on Incorporating
26 the Functional Use Approach into OPPT Activities.

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

29 ⁶ Adapted from *U.N. Global Harmonized System of Classification and Labeling of
30 Chemicals*. 2003.

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

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

34

35

1

2 **References**

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

13

14 **Glossary**

15 BBP	Benzylbutylphthalate
16 BMD	Bench Mark Dose
17 BRA	Benefit-Risk Analysis
18 BTHC	Butyryl-tri-n-hexylcitrate
19 CAS	Chemical Abstracts Service
20 CEN	European Committee for Standardization
21 CLP	Classification Labelling and Packaging regulation (EC No 1272/2008)
22 CMR	Carcinogenic, Mutagenic, toxic to Reproduction (Reprotoxic)
23 DBP	DiButylphthalate,
24 DCHP	Dicyclohexylphthalate
25 DEHP	Diethylhexylphthalate
26 DIBP	Diisobutylphthalate
27 DIDP	Di isodecyl phthalate)
28 DINCH	1,2- cyclohexan dicarboxylic acid, disononyl ester)
29 DINP	Di isononyl phthalate)
30 DIPP	Diisopentylphthalate
31 DMEP	Bis(2-methoxyethyl)phthalate
32 DNHP	Dihexylphthalate
33 DHNUF	1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters
34 DPP	Dipentyl phthalate
35 DMEL	Derived Minimum Effect Level
36 DNEL	Derived No Effect Level
37 EC	European Commission
38 ECB	European Chemicals Bureau (now ECHA)

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1	ECHA	European Chemicals Agency (formerly ECB)
2	ED	Endocrine Disruptor
3	EEC	European Economic Community
4	EMA	European Medicines Agency
5	EFSA	European Food Safety Authority
6	EN-ISO	CEN and ISO combined published document
7	FDA	Food and Drug Administration (USA)
8	ISO	International Organization for Standardization
9	LOAEL	Lowest Observed Adverse Effect Level
10	MCDA	Multi Criteria Decision Analysis
11	MDD	Medical Device Directive (Council Directive 93/42/EEC)
12	MDR	Medical Device Regulation (EU 2017/745)
13	MoA	Mode of Action
14	MoE	Margin of Exposure
15	MoS	Margin of Safety
16	NICU	Neonatal Intensive Care Unit
17	NOAEL	No Observed Adverse Effect Level
18	OECD	Organization for Economic Cooperation and Development
19	PoD	Point of departure
20	PVC	Polyvinyl chloride
21	RBC	Red Blood Cell
22	RCR	Risk Characterisation Ratio
23	REACH	Registration, Evaluation, Authorisation and restriction of Chemicals.
24	SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
25	SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
26	TDI	Tolerable Daily Intake
27	TEHTM	Tri(2-ethyl hexyl)trimellitate
28		
29		

1 **Annex 4: CMR and/or ED substances**

2
3 CMR substances are substances identified and classified as carcinogenic, mutagenic or
4 toxic for reproduction of different categories based on the intrinsic toxic properties of a
5 substance or a mixture whereof categories 1A and 1B apply to these Guidelines . In
6 Europe, classification for these endpoints is harmonised through harmonised classification
7 and labelling (CLH). Details can be found at
8 <https://echa.europa.eu/regulations/clp/understanding-clp>. For a specific substance to be
9 classified as CMR 1A, 1B or 2 a dossier needs to be prepared and if the Commission finds
10 that the proposed classification is appropriate, it submits a draft decision concerning the
11 inclusion of that substance in Part 3 of Annex VI to the CLP Regulation (Regulation (EC)
12 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures).

- 13
- 14 • Category 1A means that the substance is a known human carcinogen, mutagen or
15 reproductive toxicant based on human evidence.
 - 16 • Category 1B means that the substance is a presumed human carcinogen,
17 mutagen or reproductive toxicant based on animal studies.
 - 18 • Category 2 means that a substance is considered as suspected carcinogen,
19 mutagen or reproductive toxicant based on limited evidence from animal studies
20 or humans (not part of these Guidelines).

21

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

24 [http://www.chemsafetypro.com/Topics/EU/Annex VI to CLP: List of Harmonised Classification and Labelling for Certain Hazardous Substances.html](http://www.chemsafetypro.com/Topics/EU/Annex_VI_to_CLP:_List_of_Harmonised_Classification_and_Labelling_for_Certain_Hazardous_Substances.html)

26

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

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

32

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

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

41

42 EDs identified by the delegated act pursuant to the first subparagraph of Article 5(3) of
43 Regulation (EU) No 528/2012 concerning the making available on the market and use of

1 biocidal products, can be accessed through the Biocidal Products Committee opinions on
2 active substance approval which can be accessed via ECHA's website
3 (<https://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval>).
4

5 Substances undergoing an ED assessment under the REACH or Biocidal Products
6 regulations that have been brought for discussion to ECHA's ED Expert Group are
7 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
8 State (submitter), the outcome and the suggested follow-up for the assessment, and the
9 date of the latest update to the list entry.
10

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

16 <https://publications.europa.eu/en/publication-detail/-/publication/357b3d45-620f-11e7-9dbe-01aa75ed71a1/language-en/format-PDF>
17

18

19 In addition, Commission Implementing Decision (EU) 2018/636 identified
20 Dicyclohexylphthalate (DCHP) as substance of very high concern (SVHC) according to
21 Article 57(f) of REACH Regulation (EC) 1907/2006, due to its endocrine disrupting
22 properties with probable serious effects to humans.

23 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0636&from=EN>

1 **Annex 5: Legislation on CMR and/or ED phthalates**

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

10 Eight phthalates are also listed on the Authorisation list (Annex XIV of REACH), namely
11 DEHP, BBP, DIBP, DBP, DIPP (diisopentylphthalate), Bis(2-methoxyethyl) phthalate,
12 dipentyl phthalate, and N-pentyl-isopentylphthalate. Since February 2015 DEHP, BBP,
13 DIBP, and DBP cannot be used within the European Union without authorisation. The
14 same provision would apply to the remaining four phthalates on Annex XIV from July
15 2020. To date, applications for authorisation have been submitted for DEHP and DBP
16 only. However, imported articles do not come under the authorisation requirement. For
17 the purpose of evaluating applications for authorisation, the ECHA Committee for Risk
18 Assessment (RAC) has developed reference DNELs for several substances, including
19 DEHP, BBP, DBP, and DIPP. (See Evaluating Applications table/Reference DNELs on
20 ECHA's website: <https://echa.europa.eu/applying-for-authorisation/evaluating-applications>.)

22 REACH Annex XVII (entry 51) also restricts the placing on the market of articles
23 containing DEHP, BBP, DBP, and DIBP in concentration greater than 0.1% weight by
24 weight of the plasticised material, individually or in combination in a range of articles.
25 These articles include toys¹² and childcare articles, as well as other primarily consumer
26 and professional use articles which lead to dermal or inhalation exposure. (For risk
27 assessment conclusions, including derivation of a DNEL for DIBP, see Compiled RAC &
28 SEAC opinion and background document on ECHA's website:
29 <https://echa.europa.eu/previous-consultations-on-restriction-proposals/-/substance-rev/13919/term>.)

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

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

¹² 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).

1 of the risk assessment can be found here:

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

3 In addition to the REACH legislation, there is also product-specific legislation which
4 regulates certain phthalates, i.e. the Cosmetic Products' Regulation (EC/1223/2009) and
5 the Regulation on materials and articles intended to come into contact with food (Regulation EC 1935/2004 as general framework regulation and Regulation EU n
6 10/2011 specific for Plastic materials and articles destined to be in contact with
7 foodstuffs.) Both in the MDD (93/42/EEC) and the more recent MDR (2017/745),
8 phthalates are specifically mentioned for their use in medical devices.

9
10 For a number of phthalates there is legislation available that might contain information
11 relevant for the use of phthalates in medical devices. Of specific relevance for medical
12 devices may be the Regulation EU n.10/11, which also includes provisions for the use of
13 phthalates in food contact materials and articles with respect to migration limits. This
14 may be a parallel with migration (and thus potential internal exposure) of phthalates as
15 present in polymers used for medical device manufacturing. In Annex I of the Regulation
16 EU n.10/2011 all substances are listed, which are authorised for the use as starting
17 material or additive for plastic layers in plastic materials and articles. Each substance
18 must not exceed its specific migration limit (SML). The following phthalates and other
19 plasticisers¹³ are authorised for use as additives:

20

21 DBP (SML) = 0.3 mg/kg food

22 only to be used as:

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

26

27 BBP, SML = 30 mg/kg food

28 Only to be used as :

29 (a) plasticiser in repeated use materials and articles;
30 (b) plasticiser in single-use materials and articles in contact with non-fatty foods , not
31 for contact with infant formulae and follow-on formulae (Directive 2006/141/EC) and
32 processed cereal-based foods and baby foods for infants and young children (Directive
33 2006/125/EC);
34 (c) technical support agent in concentrations up to 0.1% in the final product.

35

36 DEHP, SML = 1.5 mg/kg food

37 Only to be used as :

38 (a) plasticiser in repeated use materials and articles in contact with non-fatty foods;
39 (b) technical support agent in concentrations up to 0.1% in the final product.

¹³ Not exhaustive examples for other than phthalates

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- 1
- 2 DINP SML = 9 mg/kg food (cumulative with DIDP)
- 3 only to be used as
- 4 (a) plasticiser in repeated use materials and articles;
- 5 (b) plasticiser in single-use materials and articles in contact with non-fatty foods , not
- 6 for contact with infant formulae and follow-on formulae (Directive 2006/141/EC) and
- 7 processed cereal-based foods and baby foods for infants and young children (Directive
- 8 2006/125/EC)
- 9 (c) technical support agent in concentrations up to 0.1% in the final product.
- 10
- 11 DIDP, SML = 9 mg/kg food (umulative I with DINP)
- 12 Only to be used as
- 13 (a) plasticiser in repeated use materials and articles;
- 14 (b) plasticiser in single-use materials and articles in contact with non-fatty foods , not
- 15 for contact with infant formulae and follow-on formulae (Directive 2006/141/EC) and
- 16 processed cereal-based foods and baby foods for infants and young children (Directive
- 17 2006/125/EC)
- 18 (c) technical support agent in concentrations up to 0.1% in the final product.
- 19
- 20 Furthermore, for DBP, BBP, DEHP, DINP, DIDP and DINCH (the latter not being a
- 21 phthalate) applies a group restriction, that is, the sum of these substances must not
- 22 exceed an SML of 60 mg/kg foodstuff.
- 23
- 24 DEHP, BBP, DBP and DIBP must not be contained in homogenous materials above the
- 25 concentration of 0.1% from July 2019 on according to the Restriction of Hazardous
- 26 Substances Directive in electrical and electronic equipment RoHS2 (2011/65/EC). For
- 27 medical devices and *in vitro* diagnostic products this restriction takes effect in July 2021.
- 28
- 29 **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 | | 84777-06-0 | Repr 1B | - |

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acid, dipentylester, branched and linear				
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

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

2 **) according to the ECHA Candidate List of substances of very high concern for
 3 Authorisation <https://echa.europa.eu/candidate-list-table>

4

5 As substances of concern, knowledge on the exposure to phthalates is important and
 6 biomonitoring of populations provides important information. For some of the phthalates
 7 already human biomonitoring assessment values, namely Biomonitoring equivalents (BE)
 8 or human biomonitoring (HBM) values, have been derived – these are concentrations of
 9 biomarkers (metabolites) in urine, which reflect an acceptable chronic exposure, since
 10 the basic assumption is an equilibrium between external exposure and internal burden
 11 (Angerer et al. 2011, Apel et al. 2017). In the course of the work done within the
 12 HBM4EU project, EU-wide health-based guidance values for the general population (HBM
 13 HBGVGenPop) and for workers (HBM HBGVworkers) could be derived for DEHP (see
 14 HBM4EU Deliverable D5.2, see <https://www.hbm4eu.eu/>).

15

1 **Annex 6: Use of phthalates in medical devices**

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

12
13 Safety concerns have been expressed for several high-risk patients groups, such as
14 neonates, infants, pregnant and breast-feeding women exposed to DEHP. The SCENIHR
15 in its Opinion of 2016 indicated that "a lack of evidence of causation between DEHP-PVC
16 and any disease or adverse effect does not mean that there are no risks". This lack of
17 evidence applies to all phthalates classified as CMR and/or identified as ED. Therefore the
18 requirement of patient subgroup analysis for the target patient groups as defined in the
19 "Intended Use" of a medical device is now included in the Regulation (EU) 2017/745.

20
21 For the use of DEHP, high risk groups were identified including patients undergoing
22 haemodialysis, extracorporeal membrane oxygenation (ECMO), and prematurely born
23 infants in Neonatal Intensive Care Units (NICU), (SCENIHR 2016). The actual exposure of
24 such patient groups relative to the toxicity including CMR/ED property needs to be
25 determined. However, even if the remaining risk is high, the benefit of the treatment
26 should be considered as well. It might be useful to evaluate the patient subgroups
27 separately:

- 28
29 • Paediatric Population (see subgroups)
30 • Peripubertal males
31 • Pregnant women
32 • Breast-feeding women
33 • any other patient group considered particularly vulnerable or exposed to high
34 levels of phthalates.

35
36 For purposes of this Guideline, the following ranges of paediatric subpopulations are
37 proposed to be used as a guide for manufacturers in medical devices (ref. SCCS Notes of
38 Guidance – SCCS/1602/18, section 3-6.9.1, page 78¹⁴)

39
40 Definition of Paediatric Population Subgroups

Paediatric Subgroup	Approximate Age Range
Full-term neonate	<1 week
Newborn	1 wk–2 months

¹⁴ https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccts_o_224.pdf

Early infant	2–6 months
Crawlers/toddler	6 months–2 years
Preadolescent	2–12 years
Adolescent	12–18 years

1

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

4

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

9

10 It should be realised that the benefit of medical devices including the use of phthalates
11 must also be considered: The survival of prematurely born infants often depends on the
12 availability of the same medical devices that result in a relatively high phthalate content
13 exposure due to treatment. Whenever possible, material with low release potential
14 should be used. (see SCENIHR opinion 2016).

15

16 Besides the direct patient benefits of the treatment with a medical device containing
17 phthalates, other functionalities may also need to be considered. For example, DEHP has
18 a stabilising effect on red blood cells (RBCs). RBCs have increased survival rates when
19 stored in DEHP containing blood bags. DEHP is incorporated into the cell walls of RBCs
20 and stabilises the membrane integrity of the RBCs. This results in a prolonged shelf life
21 and thus patient availability of blood stored in DEHP containing blood bags (SCENIHR
22 2016).

23 The plasticiser industry has been investing and developing alternatives to DEHP in
24 medical devices. Today, other plasticisers such as Di-isonyl cyclohexanoate (DINCH,
25 CAS 1166412-78-8), Tri-2-ethylhexyl trimellitate (TEHTM, CAS 3319-31-1) and Dioctyl
26 Terephthalate (DOTP, CAS 6422-86-2) are being proposed in medical applications such
27 as medical tubing and blood bags.

28 <https://www.plasticisers.org/applications/medical-applications/>

29

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

33

34

35

1 **Reference**

2

3 Huntley P, Editor The classified phtalates should be phased out of medical devices.
4 Program Meeting on Alternatives to Classified Phthalates in PVC Medical Devices
5 Conference; 2014 Mar 27; Copenhagen, Denmark. (<https://pvc.dk/wp-content/uploads/2016/02/pvc-alternativer-til-klassificerede-ftalater-program.pdf>)
6

7

8

9

1 **Annex 7: Approaches for Benefit-Risk Assessment**

2

3 Several approaches for BRA have been proposed especially in the context of medicinal
4 products. The Innovative Medicines Initiative PROTECT Project (www.imiprotect.eu),
5 presented a detailed review of approaches used for BRA (Mt-Isa et al. 2014). In this
6 review, 47 approaches were identified and classified as descriptive (qualitative or semi-
7 qualitative) or quantitative frameworks (relying on quantitative methods of trading risks
8 and benefits following mathematical principles), metrics (measures for benefits and risks
9 that are usually endpoint specific), estimation techniques (i.e., simulation techniques and
10 meta-analysis), and utility survey techniques (to elicit stakeholders' preferences).

11

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

17

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

24

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

35

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

41

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 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 potential alternative(s); Step 7: Assessment of the risk of identified potential 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 alternatives; Step 9: Comparison of risk(s) of original CMR/ED phthalate as used in the medical device with risk(s) of identified potential alternatives; and Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified potential 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.

1

2

3 **References**

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