European Commission

The European Commission's Scientific Committees

WG on Benefit Risk Assessment (BRA) of Phtalates in Medical devices (guidelines)

Health and Food Safety

European Commission

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Expertise covered

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Toxicology including regulatory toxicology and risk assessment
Safety evaluation Medical Devices
Risk Assessment Medical Devices
Medical Device material chemistry
Clinical use of Medical Devices
Phthalates as endocrine disruptors
Regulatory use restriction of phthalates
Exposure assessment to chemicals released from Medical Devices
Analytical chemistry of plasticizers
Benefit risk assessment methodologies
Biostatistics and epidemiology

Mandate

Request for guidelines:

On the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting properties.

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MDR 2017/745

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

Accordingly, Section 10.4 of Annex I, which deals with **substances** in medical devices, states that *"Devices shall be designed and manufactured in such a way as **to reduce as far as possible the risks posed by substances or particles**, including wear debris, degradation products and processing residues, that may be released from the device."* Particular substances of concern are those which (a) are carcinogenic, mutagenic or toxic to reproduction (**CMR**), of category 1A or 1B,2 or (b) have endocrine-disrupting properties (**ED**).

Devices…… shall only contain any such substance above the concentration of **0.1% weight** by weight where **justified** pursuant to Section 10.4.2

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Scientific Committee on Health, Environmental and Emerging Risks

SCHEER

PRELIMINARY version of the

Guidelines

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

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The guidelines

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

These Guidelines do not provide information for the BRA of the use of a medical device itself. For the BRA of medical devices in general, elements of guidance are available in section A7.2. of MEDDEV 2.7/1, revision 4. Additional information may be found elsewhere, for example in the following documents FDA 2016, 2018, EN ISO 14971[2], ISO/TR 24971. It should be noted that the acceptability of any risk is evaluated in relation to the benefit of the use of the medical device.

Definitions

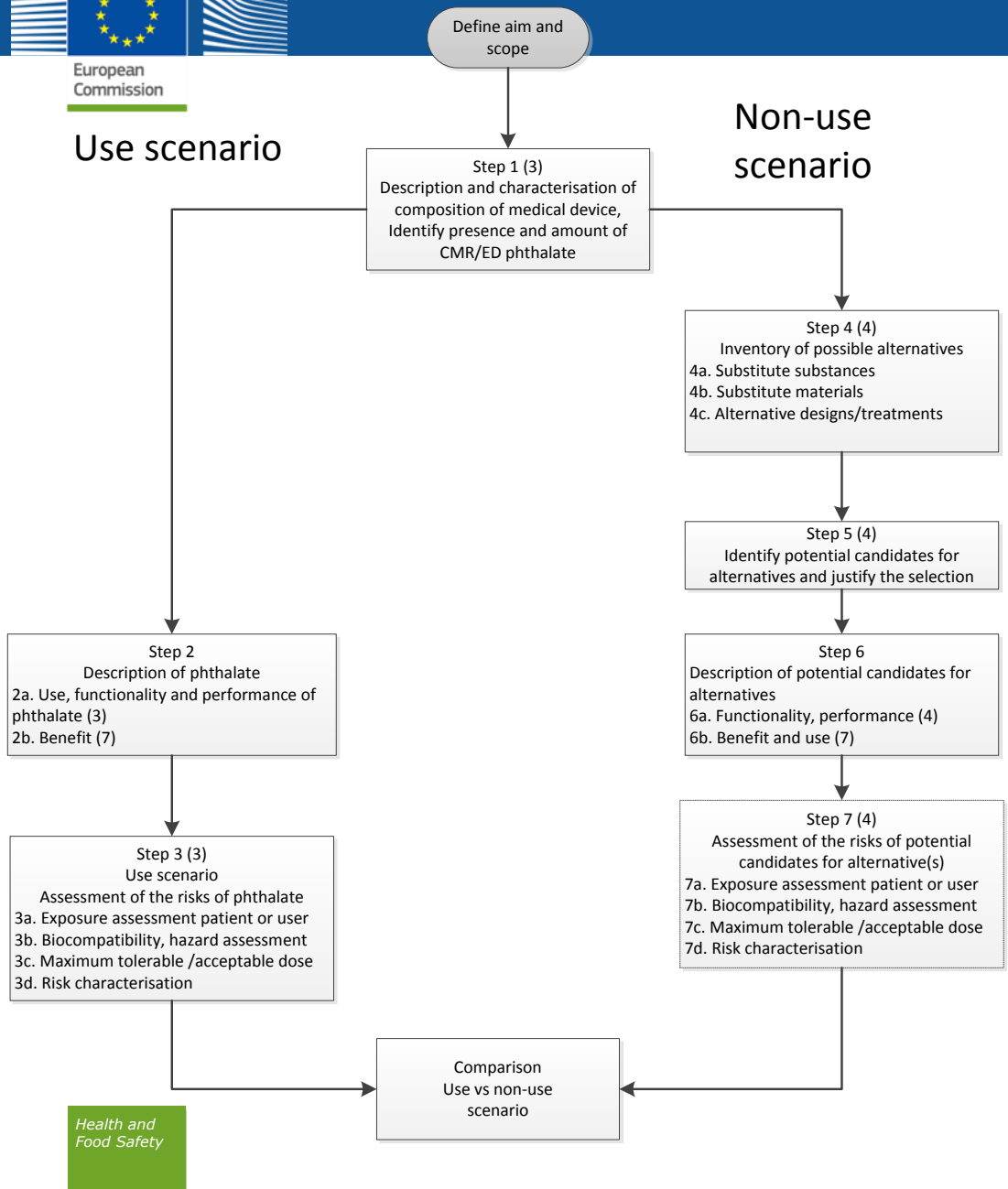
For the purpose of this guideline the following definitions are used:

*"**Alternatives** are defined as substances, materials, designs and medical treatments that can be used to replace the use of CMR and/or ED substances in medical devices".*

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

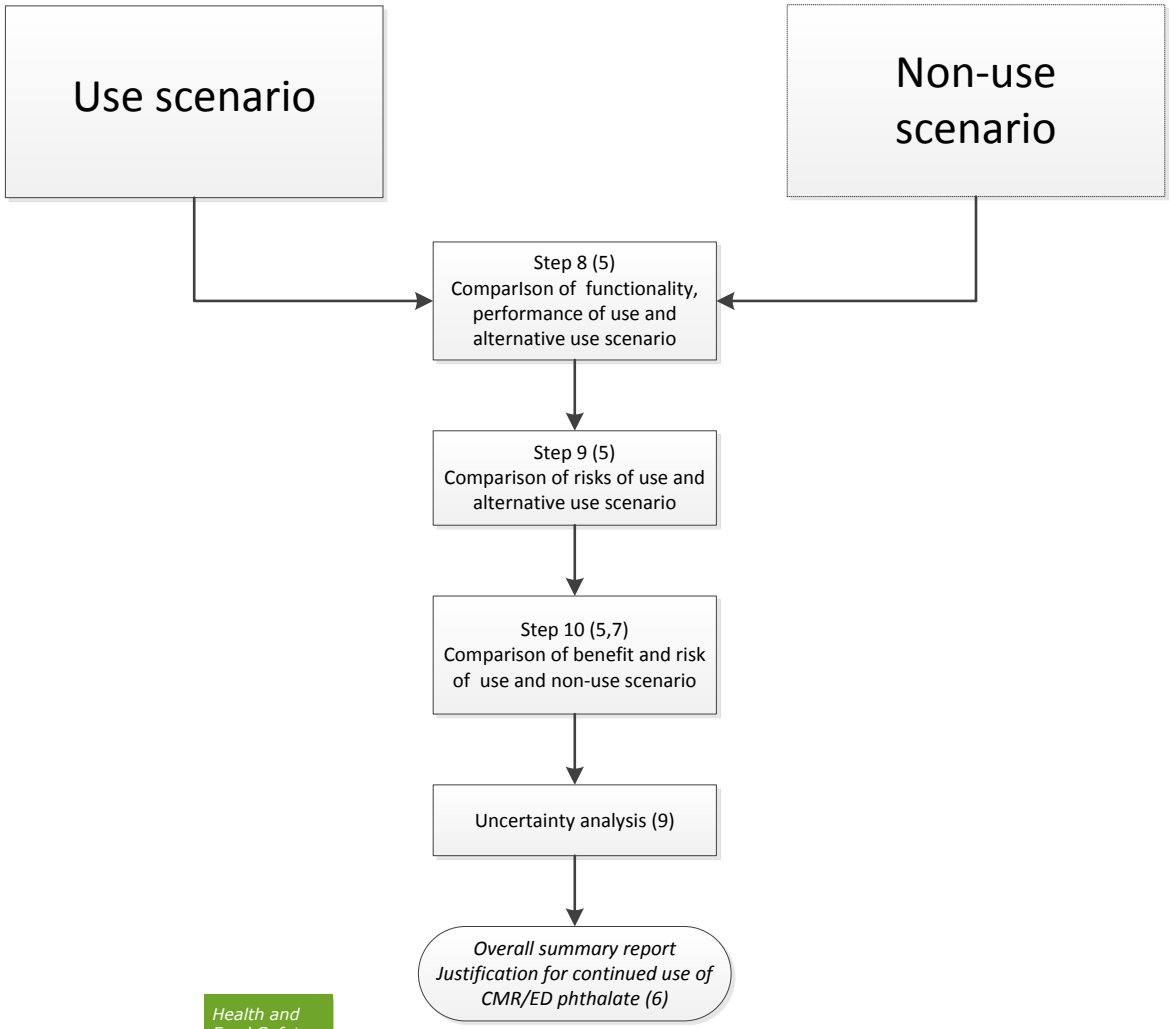
Flow chart for benefit risk analysis for evaluation of use of CMR/ED substances in medical devices.

Part 1 Information gathering



Flow chart for benefit risk analysis for evaluation of use of CMR/ED substances in medical devices.

Part 2 Comparison/justification use of CMR/ED phthalate



Stepwise approach

Step 1: Description and characterisation of the composition of the medical device. Identify presence and concentration of ***CMR/ED phthalates****.*

Step 2: Use and functionality of the phthalate

Step 3: Assessment of the risk of the CMMR/ED phthalate

- *3a. determination patient exposure based on realistic worst case use scenario*
- *3b. identification biocompatibility, general toxicological and specific CMR/ED hazards associated with the phthalate*
- *3c. determination maximal tolerable/acceptable exposure for patient based on pre-clinical and clinical information*
- *3d. determination risk for various use scenarios and patient groups*

Step 4: Inventory of possible ***alternatives***

- *4a. substances*
- *4b. biomaterials*
- *4c. Designs and/or medical tretaments*

Step 5: Identification candidates for assessment as potential alternatives and justification of selection/exclusion of possible alternatives

Step 6: Description of identified potential alternatives

- *6a functionality and performance*
- *6b benefit*

Step 7: Assessment of risk identified potential alternatives

- *7a. determination patient or user exposure based on realistic worst case use scenario*
- *7b. determination toxicological and CMR/ED hazards associated with the alternative*
- *7c. determination maximal tolerable /acceptable dose of alternative for patient*
- *7d. determination risk potential alternatives for various use scenarios and patient groups*

Description of risk

Based on exposure levels

- Derived No Effect Levels (DNEL) for threshold substances
- Derived Minimum Effect Levels (DMEL) for non threshold substances
- Acceptabel Daily Intake (ADI)
- Tolerable Daily or Weekly Intake (TDI, TWI)
- Margin of Exposure (MoE)
- Margin of Safety (MoS)

Comparison phthalates vs alternatives

Step 8: Comparison functionality and performance of CMR/ED phthalate with identified potential alternatives

Step 9: Comparison risk(s) original CMR/ED phthalate with risk(s) of identified potential alternatives

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

Prepare overall summary report

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Justification use of CMR/ED phthalate

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

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Aspects to consider for comparison

Functionality

Performance

Clinical benefit/performance

Concentration (exposure)

Leaching from medical device (exposure)

Exposure estimation

Hazard identification

Risk Assessment, Point of Departure (PoD) (LOAEL, NOAEL, BMD, T25, BMD10)

Confidence estimation

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Justification use of CMR/ED phthalate

When the outcome of the comparison shows that the alternative fulfils a comparable or better intended functionality as well as performance and shows reduced risk, the use of the CMR/ED phthalate is not possible.

When the potential alternative fails in any of the parameters such as functionality, performance, and the benefit-risk ratio or profile the conclusion can be drawn that the use of the proposed CMR/ED phthalate is justified.

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Table 2 Approximate probability scale

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

Guidelines content

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3 Assessment of the presence of a phthalate in a medical device

4 Assessment of possible alternative substances, materials, designs or medical treatments

5 Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates

6 Justification for the use of CMR/ED phthalate

7 Benefit assessment

- 7.1 Material benefit
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9 Uncertainty analysis

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B. REFERENCES

C. ANNEXES

Annexes

Annex 1 SCHEER Mandate guidelines for BRA phthalates

Annex 2 MDR 2017/745 regulation article adressing substances

Annex 3 definitions/descriptions –references-glossary

Annex 4 CMR and/or ED substances

Annex 5 Legislation on CMR and/or ED phthalates

Annex 6 Use of phthalates in medical devices

Annex 7 Approaches for Benefit Risk Assessment

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Questions ?

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Expertise covered

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SCHEER and SCCS experts

TV Toxicology, RA

DP Epidemiology, Biostatistics

TB Toxicology, RA, exposure, toxicology, ED

ET RA, toxicology MD

WDJ RA, safety MD

RMI RA, toxicology, ED

CR RA, toxicology, ED

UB RA, exposure, ED

EU Agencies advisors

KV Toxicology, phthalates

ES Toxicology, phthalates

FP Medical doctor, biostatistics

External experts

HK Material science, MD

TS Clinician, MD, Statistics

MRM Toxicology, phthalates