The European Commission's Scientific Committees

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

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.
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
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
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 treatments

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
- Acceptable 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
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**.
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
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.
**Table 2 Approximate probability scale**

<table>
<thead>
<tr>
<th>ISO probability term</th>
<th>Subjective probability range</th>
<th>Probability term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td>&gt;90%</td>
<td>Very likely</td>
</tr>
<tr>
<td>Probable</td>
<td>66%-90%</td>
<td>Likely</td>
</tr>
<tr>
<td>Occasional</td>
<td>33%-66%</td>
<td>As likely as not</td>
</tr>
<tr>
<td>Remote</td>
<td>10%-33%</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Improbable</td>
<td>&lt;10%</td>
<td>Very unlikely</td>
</tr>
</tbody>
</table>
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Questions
Expertise covered

**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**

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ES  Toxicology, phthalates
FP  Medical doctor, biostatistics

**External experts**

HK  Material science, MD
TS  Clinician, MD, Statistics
MRM  Toxicology, phthalates