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*

MedTech Europe comments

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Applicability of the Guidelines (1)

- The preliminary Guidelines do not specify that the requirement for benefit-risk assessment is limited to those devices described in MDR Annex I Sections 10.4.1. (a) and 10.4.1. (b):

> *Devices, or those parts thereof or those materials used therein that:*
>
> *— are invasive and come into direct contact with the human body,*
>
> *— (re)administer medicines, body liquids or other substances, including gases, to/from the body, or*
>
> *— transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body*

- MedTech Europe would like the Guidelines to mention clearly that, in line with the MDR legal text, benefit-risk assessment is only required for these specified devices/components, and not for other contact/surface materials.

Applicability of the Guidelines (2)

- Benefit-risk assessment (BRA) is a general methodology not specific to phthalates and guidelines already exist. In turn, the BRA for phthalates would not be different than a BRA for other hazardous substances regulated under the MDR.

- Within the draft Guidelines, there does not appear to be much value added from any reference to phthalates or the provided information on phthalates (*e.g.,* within the Annexes).

- MedTech Europe therefore recommends that the Guidelines be generalised to all substances referenced in MDR Annex I Sections 10.4.1. (a) and 10.4.1. (b) unless it is the intention to regulate phthalates differently.

Alternatives Assessment (1)

- Several statements throughout the preliminary Guidelines suggest that 'prototype' devices made with the alternative would be required to complete the BRA, *e.g.*:
  - *"The functionality and performance of the alternative shall be comparable to the extent that there would be no clinically significant difference in the performance of the device... Considerations of functionality and performance shall be based on proper scientific justification."*
  - *"[T]here is a considerable lack of data for potential alternatives to be used in medical devices. Therefore, manufacturers are encouraged to produce quantitative data on the use of alternatives for CMR/ED phthalates in medical devices."*
- These statements suggest that the medical device industry should make 'prototype' devices to understand leaching (exposure), biocompatibility, functionality, and (clinical/product) performance of the device constructed with the alternative in comparison to the device with the CMR/ED substance.
- Can clarification on this expectation be provided?

Alternatives Assessment (2)

- The preliminary Guidelines do not consider the possibility that the use of the CMR/ED substance presents no-to-negligible risk, thereby precluding the need to assess the benefit of the device with the CMR/ED and/or the device constructed with the alternative.
  - *"[A]cceptability of any risk is evaluated in relation to the benefit of the use of the medical device"*
  - *For such a justification several steps need to be considered including the possible use of alternative substances, materials…"*
- If there is no-to-negligible risk associated with the use of a CMR/ED substance present in a device above 0.1% (w/w), why would benefit need to be addressed? In this case, the benefit will always outweigh the risk.
- If the safety of using the CMR/ED can be proven (*i.e.,* no-to-negligible risk exists), is assessment of potential alternatives (non-use scenario) required?

Alternatives assessment (3)

- It is unclear what is meant by ‘large benefit’ and ‘absence of toxicity’ in the below statement. Can this be clarified?
  - *“A slight clinically insignificant loss in functionality might be acceptable if there is a large benefit to be gained in terms of reduced or even absence of toxicity.”*
- Should ‘absence of toxicity’ be ‘absence of risk’?
- If the use of the CMR/ED substance is considered safe (< agreed threshold), how ‘large’ should the benefit be to favour the alternative?
- What is a ‘*slight clinically insignificant loss in functionality*’?
  - *i.e.,* how ‘slight’ should the ‘loss of functionality’ be to favour the alternative?
- Can quantitative definitions be provided for this statement?

Definition of ‘Acceptable Risk’

- Throughout the Guidelines, clarification as to what ‘acceptable risk’ means is needed; *e.g.*:
  - *“**Determine** and describe in which situation the risk can be <u>acceptable</u> for the use of the CMR/ED phthalate in the medical device.”*
- Can acceptable risk be defined as:
  - 10^{-6} – 10^{-4} risk for non-threshold carcinogens
  - Margin-of-safety > 1
  - Hazard index < 1
- The preliminary Guidelines also refer to REACH terminology (DNELs – Derived No-Effect Level – and RCR – Risk Characterisation Ratio). Is there a preference for a specific value?

Classification of Risk

- Throughout the preliminary Guidelines, the possibility that the risk of using a CMR/ED substance and the risk of using an alternative could be equivalent does not appear to be acknowledged; *e.g.*:
  - *"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 argumentation why possible alternatives are appropriate or inappropriate…"*
  - *"However, for it to be suitable, the potential alternative must represent a reduction in the overall risks to human health…"*
- This may be due to the absence of risk classification within the preliminary Guidelines.
  - Can risk be classified into categories (negligible, low, medium, high), (*e.g.*, comparable to control banding system under EU Occupational Safety & Health legislation)? If so, the CMR/ED and the alternative may have identical risks (*e.g.,* negligible).
  - In this case, can the conclusion be that the risk is equivalent and, in turn, there is no change to the risk?

Consideration of Exposure and Hazard when Evaluating Risk

- In several places, the preliminary Guidelines mention the evaluation of hazard or *"risk in terms of hazards".*

- Risk = hazard x exposure; *i.e.,* risk is expressed in terms of hazard and exposure. The value of evaluating hazard, especially in the context of safety risk, is unclear; *e.g.*:

  - An alternative may have a different hazard than a CMR/ED, but the exposure to both may be non-existent resulting in no risk.

  - In this case, hazard x exposure (value equals zero) = no risk, and the consideration of hazard alone would not seem to be relevant.

- The MDR specifically mentions exposure (Annex I Section 10.4.2. (a)), which suggests that risk is a more important consideration than hazard when evaluating safety per the Regulation. Could the Guidelines confirm that exposure, in addition to hazard, should be considered when risk is being evaluated?

Relevant Endpoints of Consideration

- It appears that the preliminary Guidelines want industry to justify the presence of a CMR/ED substance based on an endpoint (*e.g.,* most sensitive) that is different than endpoints for CMR/ED. Can clarification be provided?
  - *"Describe hazards associated with the CMR/ED phthalate by considering all relevant toxicological endpoints for acute as well as for repeated dose toxicity…such a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest observed-adverse-effect-levels (LOAEL)..."*
- Data present in the biocompatibility evaluation of the device (*e.g.,* risk assessment and/or *in vivo* testing) meets this request, but for some devices, may not speak to the risk of CMR/ED effect occurring.
- If the exposure is above that considered safe for the most sensitive endpoint, yet the device passed *in vivo* testing for that endpoint, an evaluation of whether the exposure elicits a CMR/ED effect may still be warranted.
- Furthermore, if the safety evaluation of a CMR/ED containing device is based on endpoints other than CMR/ED, why are CMR/EDs not being regulated on whether the device containing them passed biocompatibility testing?

Scenarios for Exposure Analysis

- What is meant by “realistic worst-case scenario”?
  - *“3a. Determination of the patient exposure based on realistic worst-case[3] use scenario in the intended use.”*
- Can a variety of options for analysing exposure be provided in the Guidelines (*e.g.*, the option to evaluate true exposure)?:
  - Exposure assessment under realistic simulated-use scenarios (see ISO 10993-12).
  - Extractables & leachables analysis (ISO 10993-18) or a non-volatile residue test (USP <661>) for accurate exposure information.

Biomonitoring Data

- The utility of biomonitoring data for the justification of a CMR/ED is unclear.
  - *"[D]ata from biomonitoring programs may become available that could also provide information on exposure levels of phthalates."*
  - *"For some of the phthalates already human biomonitoring assessment values, namely Biomonitoring equivalents (BE) or human biomonitoring (HBM) values, have been derived – these are concentrations of biomarkers (metabolites) in urine, which reflect an acceptable chronic exposure, since the basic assumption is an equilibrium between external exposure and internal burden (Angerer et al. 2011, Apel et al. 2017)."*
- Biomonitoring data provides body burden values for specific chemicals; in most cases, the source of the exposure (*e.g.*, a manufacturing site) is known.
- Where should this biomonitoring data come from?
- How can we ensure that the BE values mentioned above are from relevant sources (*i.e.*, the medical device of interest) and not from other, non-relevant sources (exposome)?

Uncertainty Analysis

- Section 9. Uncertainty Analysis is one of the longer sections of the preliminary Guidelines.
- If uncertainty is such a large part of the approach outlined in the Guidelines, it suggests that a better approach is warranted, one with considerably less potential for uncertainty?
- As much of the analysis could be based on expert judgment and assumptions using literature data, can clarification be provided on the request to include statistical approaches and uncertainty analysis?
- What is meant by “non-standard uncertainties”?

Thank you for your attention

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