GMED LNE GROUP Newsletter

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PHTHALATES IN MEDICAL DEVICES: REGULATIONS AND ALTERNATIVES

Since the early 2000s, particularly in Europe, there has been a growing awareness of the impact of chemical substances on the environment and human health, including their long-term or unknown effects. The SCENIHR 2008 report flagged risks such as endocrine disruption and reproductive toxicity, especially in vulnerable populations. Its 2015 update reinforced these findings and emphasized on safer alternatives. The SCHEER report expanded on environmental impacts and lifecycle risks, advocating for regulatory action.

To ensure a high level of protection for human health and the environment, the European Union (EU) adopted the Registration, Evaluation, Authorization, and Restriction of Chemicals Regulation (Regulation (EC) 1907/2006 - REACH) in 2006, which came into force in 2007 with the establishment of the European Chemicals Agency (ECHA). REACH applies to all chemical substances and affects most companies across the EU, including those importing chemicals for food containers, toys, medical devices, and other consumer goods. Additionally, REACH aims to foster innovation and competitiveness by evaluating safer alternatives, promoting non-animal testing, and bringing together expert groups.

This newsletter focuses on phthalates such as di-(2-ethylhexyl) phthalate (DEHP). These chemicals are used as plasticizers to soften and increase the flexibility of plastics, particularly polyvinyl chloride (PVC). DEHP and other phthalates are on the REACH list of Substances of Very High Concern (SVHC).

A PHTHALATES IN MEDICAL DEVICES

Phthalates are used in medical devices such as blood bags, tubing, catheters and disposable gloves to make materials more pliable and comfortable to use. The concentration depends on the purpose. For example, the typical concentration of DEHP in plasticized PVC is 40% by weight (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans). Total plasticized PVC in medical devices in Europe is approximately 3000 tons annually.

Phthalate plasticizers do not chemically bond to PVC plastic and, therefore, can leach out. For example, DEHP can be released from blood plastic bags into blood components, potentially infusing into the blood donor during apheresis collections or into the patient during a transfusion. Other than improving flexibility of blood bags, it can also offer some benefits through enhancing the morphology, deformability, and osmotic fragility of stored red blood cells, ensuring their functionality during transfusion (Almizraq et al. 2018).

While some phthalates can offer these benefits, their use is associated with health risks, including reproductive and developmental toxicity as well as disruption to the endocrine system (C(2017) 4462)

This has led to increased regulatory scrutiny and the search for safer alternatives, particularly for use in medical devices. Medical devices made from plasticized PVC, or any other SVHC must not only comply with medical device directives and regulations but also require the manufacturer or importer of the chemical substances to register the substance and its quantity with the ECHA.

With the amendment to the Regulations (EU) 2017/745 (MDR) and (EU) 2017/746 (IVDR), the European Commission has revised Regulation (EC) 1907/2006, extending the use of DEHP in medical devices ((EU) 2023/2482). Initially, in accordance with Article 57(1) of Regulation (EC) 1907/2006, such uses of DEHP were not allowed after the sunset date, May 2025.
However, the latest application date for the uses of DEHP in medical devices is now January 1st, 2029, with an extension of the sunset for DEHP use to July 1st, 2030.

B PHTHALATES ALTERNATIVE

The management of the use of phthalates in medical devices will involve risk management, evaluating the benefit-risk ratio, considering the patient population and exposure levels, and finally reviewing the information provided by the manufacturer to both patients and healthcare professionals. The extension of the use of DEHP provides manufacturers with an opportunity to test and incorporate alternatives, supported by sufficient data from independent research peer-reviewed studies, and scientific opinions.

If phthalates such as DEHP are replaced by an alternative plasticizer, their functionality and safety must be assessed and tested specifically for targeted populations, such as children, pregnant or breastfeeding women, and other patient groups considered particularly vulnerable to such alternative substances and materials. ECHA and EU Member States play a role in the scope of REACH to evaluate information provided and authorized replacement to SVHC with technical and economical assessment data review.

C OBLIGATION OF THE MANUFACTURER

In any case, the design and manufacturing of medical devices and in-vitro diagnostic medical devices should aim to minimize risks as much as possible.

Should in-vitro diagnostic medical devices contain a substance or a mixture which may be considered as being dangerous, taking account of the nature, quantity, form of its constituents, relevant hazard pictograms, and labelling requirements of Regulation (EC) 1272/2008 shall apply, as per 20.1 (i) chapter III of Annex I of IVDR.

For medical devices, the presence of hazardous phthalates, such as DEHP, in a concentration above 0,1 % weight by weight (w/w) in a medical device, must be appropriately labelled as referred to in 10.4.5 Chapter II of the General Safety and Performance Requirements (GSPR) of MDR. Additionally, if the device is intended for use in children, pregnant or breastfeeding women, or other vulnerable patient groups, the instructions for use must include information on any residual risks for these specific populations.

If DEHP is maintained in the medical device, the manufacturer will have to submit an application to ECHA to use DEHP until the sunset date July 1st, 2030.

D GUIDELINES ON BENEFICE-RISK ASSESSMENT OF THE PRESENCE OF CRM/ED PHTHALATES IN MEDICAL DEVICES (SCHEER, 2024)

1. Scope

In conformance with GSPR 10.4. "Substances" of MDR, this guidance covers the devices, or parts thereof, or those materials used therein, which:
- Are invasive and come into direct contact with the human body, or;
- (Re)administer medicines, body liquids or other substances, including gases, to/from the body, or;
- Transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body.

The guidance aims, for an individual device, to:
- Analyse and estimate potential patient or user exposure to the substance;
- Analyse possible alternative substances, materials, designs, or medical treatments;
- Justify why possible substance and/or material substitutes, or design changes, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the medical device, taking into account its intended use and clinical population(s), in particular the vulnerable ones to such substances and/or materials.

These guidelines are intended to be used by the relevant stakeholders (manufacturers, notified bodies and regulatory bodies...) and the recommended methodology is based on horizontal standards and state of the art in terms of Risk Management, Toxicological Risk Assessment, Clinical Evaluation.

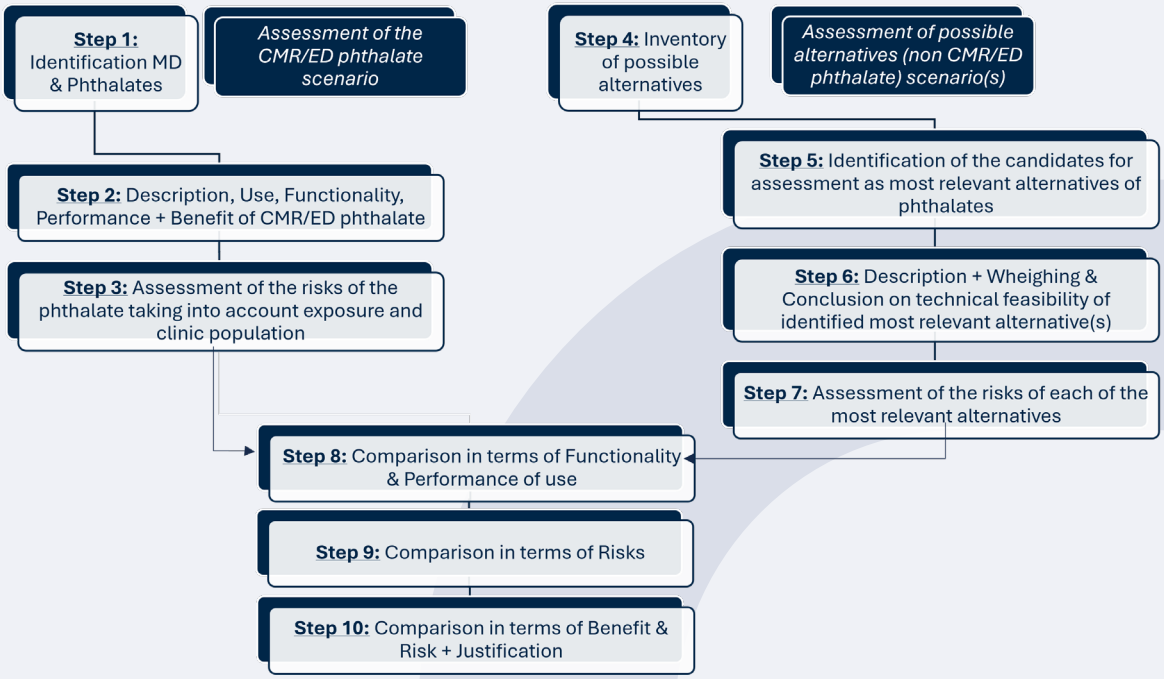
2. Définitions

"CMR substances" are substances identified and classified as carcinogenic, mutagenic or toxic for reproduction. They are classified into different categories based on the intrinsic toxic properties of a substance. In Europe, classification for these endpoints is harmonized. Categories 1A (known human CMR substances) and 1B (presumed human CMR substances) apply to these guidelines (see Part 3 of Annex VI of Regulation (EC) 1272/2008).

"Endocrine Disruptors" (ED) are substances or mixtures that alter one or more functions of the endocrine system and consequently cause adverse effects in an intact organism, its progeny, populations, or subpopulations. Regulation (EU) 2023/707 amending Regulation (EC) 1272/2008 classifies now ED substances into two categories based on the level of hazard evidence: known or presumed endocrine disruptors (Category 1) and suspected endocrine disruptors (Category 2), both for human health and for the environment (see Annex I, Table 3.11.1. of Regulation (EU) 2023/707).

"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.

3. Guidelines



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Conclusion

The MDR and IVDR aim to ensure the safety and performance of medical devices while minimizing potential health risks associated with hazardous substances like DEHP. The requirements of REACH and the GSPR, the modification of regulations and the delay of the sunset of DEHP, among others, in Europe should encourage manufacturers to find safe alternatives to the chemical components. This aligns with the key insights from the SCENIHR and SCHEER reports, which emphasize the need for safer substitutes, reduced environmental impacts, and compliance with evolving regulatory frameworks to safeguard public health and drive innovation.

To go further

TRAININGS FOR AMERICA REGION

Cleanliness of Newly Manufactured Medical Devices
1.5-day training session | In-Person Training

→ CHECK OUT THE PROGRAM

TRAININGS FOR OTHER REGIONS

Apply the requirements of European Regulation 2017/745 on medical devices
SA56 | 2 days | Virtual Classroom

→ CONTACT GMED TRAINING CENTER

Drawing up technical documentation in compliance with Regulation (EU) 2017/745
SA57 | 1.5 days | Virtual Classroom

→ CONTACT GMED TRAINING CENTER

Biological evaluation of medical devices
SA21B | 2 days | Virtual Classroom

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