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Phthalates and endocrine disruptors:

An overview of their safety requirements and evaluations together with the standards that support them

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Glossary

Term	Lay explanation
Absolute toxicity	Toxicity without considering dilution
AET	Analytical Evaluation Threshold. Threshold below which the analyst need not identify or quantify leachables or extractables or report them for potential toxicological assessment
ALARP / ALARA	'As low as reasonably practicable' or 'as low as reasonably achievable'
Benchmark dose	A dose linked with a specified level of response; a dose corresponding to a specified level of risk, generally in the range of between 1% to 10% deviation of a control value. Can be indicated by its low or high confidence limit, i.e. Benchmark Dose low or Benchmark Dose high
Bolus dose	A quantity of agent administered all at once, usually applied to the single daily parenteral administration of a medicine
BRA	Risk/benefit analysis part of the risk management analysis
CLP	Classification, Labelling & Packaging (CLP) Regulation 1272/2008
CMR	Substances identified as carcinogenic, mutagenic or toxic for reproduction
Coexposure	Exposure to multiple compounds that may have the potential to cause additive or synergistic effects and further disrupt human metabolism; the 'cocktail effect'
Clinically established	Medical device, component, or material of construction which has been used extensively for specified and established clinical uses for which biocompatibility has been established
ECHA	European Chemicals Agency
ED	Endocrine disruptor / Endocrine-disrupting substance
EDC	Endocrine-disrupting chemical
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EN ISO 3826-1	European and international ISO standard entitled: Plastics collapsible containers for human blood and blood components — Part 1: Conventional containers (2019)
Extractable	Any substances that can be released from a medical device or material using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the conditions of clinical use (ISO 10993-12)
FAO	Food and Agriculture Organization of the United Nations
GSPR	General Safety and Performance Requirements
ICH Q3A / Q3B	International Council for Harmonization (ICH) Q3A / Q3B Guidelines which cover impurities in new drug substances / drug products
ICH Q3C / Q3D	International Council for Harmonization Guidelines that cover residual solvents in pharmaceutical products / elemental impurities
Internal dose	The absorbed dose

Glossary

Term	Lay explanation
IPCS	International Program on Chemical Safety
ISO 10993-1	Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process (2018)
ISO 10993-12	Biological evaluation of medical devices — Part 12: Sample preparation and reference materials (2012)
ISO 10993-17	Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances (2002)
ISO 10993-18	Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process (2020)
ISO 14971	Medical devices — Application of risk management to medical devices (2019)
Leachable	Substances that can be released from a medical device or material during clinical use (ISO 10993-12)
LOQ	Limit of Quantification. The lowest analyte concentration that can be quantitatively detected with a stated accuracy and precision
Medical device configuration	Listing of a medical device's components (qualitative), including a listing of the component's materials of construction (qualitative) and the proportion of each material in each component (quantitative)
MDR	European Medical Devices Regulation 2017/745
Obesogen	Foreign chemical that disrupt the balance of lipid metabolism and which can lead to obesity in some patients
OECD	Organisation for Economic Co-operation and Development
PFAS	Per- and polyfluoroalkyl substances
PQRI	Product quality research institute
Qualification	Process of establishing that an analytical method is suitable for its intended use
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SCT	Safety Concern Threshold. Threshold below which a leachable (or an extractable as a probable leachable) has a dose so low that it presents a negligible safety concern from carcinogenic and non-carcinogenic toxic effects
Sertoli cell	A nurse cell for the outer surface lining of the blood-testes barrier
Slope	The difference in the incidence or magnitude of an effect divided by the difference in dose that created the effect
SVHC	Substances of very high concern [under Article 57(c) of REACH Regulation (EC) 1907/2006]; listed in Annex VI of the CLP Regulation
Synergism	A phenomenon in which the toxicity of a mixture of chemicals is greater than that would be expected from a simple summation of the toxicities of the individual chemicals present in the mixture
Thyroglobulin	A protein made by cells in the thyroid gland
Thyroid	The thyroid gland is a hormonal gland in the neck. It produces two hormones (T3 and T4) that are secreted into the blood so that the cells in the body work normally
TI	Tolerable intake after modification based upon the toxicity evaluation of a chemical/compound; expressed in milligrams per kilogram body mass per day
TTC	Threshold of Toxicological Concern. Level of exposure for constituents, below which there would be no appreciable risk to human health
UNEP	United Nations Environment Programme
USP	U.S Pharmacopeia
WHO	World Health Organization
Xenobiotic	An agent that is foreign to the body; a substance that is usually not present in the reference organism; a chemical, synthetic in origin that is damaging to a biological system

Overview

Phthalates are plasticizers that impart flexibility to plastic products and can leach into their surroundings. Regulatory requirements for medical devices (MDs) include special requirements for MDs to be used safely in their clinical setting. When there are changes to the clinical use of an existing product such as increasing duration of use, new routes of administration or new patient subpopulations, or design and material composition changes, that may impact former assessments, a new assessment is expected to be performed to demonstrate safety.

The new regulatory requirements (European Medical Devices Regulation 2017/745 (MDR)) relate both to general safety and performance requirements for the products, including dedicated evaluations of phthalates and endocrine-disruptors' in medical devices for achieving safety.

With phthalates, many have the potential to cause hormonal disruption, however, it was only recently (January 2020) that experts produced a useful consensus paper (La Merrill et al., 2020) which defined the key characteristics of endocrine-disrupting (ED) chemicals as a basis for the identification of their intrinsic hazard.

The regulatory requirements aim to diminish the use of endocrine-disruptors in MDs, and accordingly, this involves:

- Identifying scientifically-recognized ED substances
- Implementing and maintaining general safety and performance requirements
- Defining clinically-relevant health effects
- Deriving safety margins for particular health conclusions
- Evolving sequential chemical assessment, substitution and resolution

This paper provides an overview of these safety requirements and evaluations.

Introduction

This white paper summarizes the evaluation of phthalates and ED substances in medical devices (MDs). These substances are referred to as substances of very high concern (SVHC). The overall purpose of this paper is to describe and examine how particular scientific assessment criteria can be used to evaluate MDs for ED potential.

The MDR includes the general safety and performance requirements (GSPRs) in Annex I related to design and manufacture. In 2017, the MDR introduced new requirements related to safety and performance. The first article of Annex I 'General Requirements' states that any risk which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient.

Additionally, the MDR also triggers a comprehensive program to re-evaluate the safety of more than 1,100 substances as MD constituents. In fact, these MD constituents include extractable constituents that may migrate into the drug product (DP) when these are stored within an MD, such as blood bags and syringes. Therefore, to place an MD on the market, the manufacturers must demonstrate safety and performance for professionals and patients within the context of a benefit-risk ratio.

Elements that are fundamental to the safety evaluation of MDs include requirements regarding design and manufacture, and the lack of or presence of toxic substances with a special emphasis on phthalates, CMR and ED substances. This underpins exposure assessment, guidelines on phthalates, labelling guidelines, influence of metabolism, and the study of toxicological mechanisms of these substances.

This document intends to provide useful insights into how phthalates and ED substances are evaluated for safety, following the relevant guidelines and horizontal risk management standards (ISO 14971:2019 and ISO 10993-1:2018).

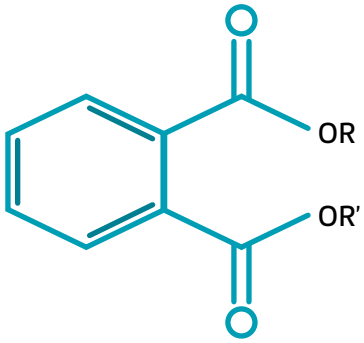
Guidelines as to how to evaluate the possible alternatives to CMR phthalates are presented in a recent opinion by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER, 2019).

Phthalates utilised in medical devices

Phthalates represent a class of high production volume chemicals that can alter reproductive development. Phthalate esters are plasticizers that impart flexibility to plastic products.

As the phthalate is not chemically bound to the polymer matrix, the phthalate ester (Figure 1) can be released from the polymer and leach into the surrounding environment, including the body of a patient.

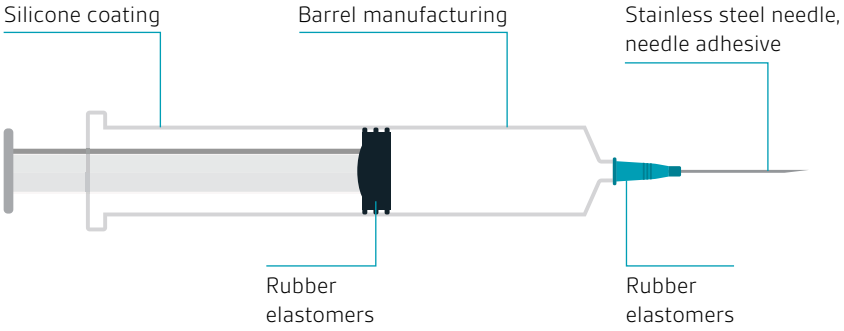
Figure 1. The phthalate ester



Multiple types of materials are used in primary containers and drug delivery MDs, such as prefilled syringes. Prefilled syringes are utilized for small- and large-volume parenteral dosing to patients which may receive multiple doses per day (Figure 2).

Phthalates are abundantly used in plastic blood bags and tubing in the hospitals.

Figure 2. A prefilled syringe system utilised as a drug delivery system



Furthermore, were the prefilled syringes to incorporate a medicinal product as an integral part of the product, it will comply with the Medicines Regulation for marketing authorization and the MD part of the product will fulfill the GSPRs in the MDR. Thereupon, it will not be CE-marked.

Extractables studies provide useful information on the characterization of materials and for the predictive forecasting of potential constituents which have the capacity to leach from MDs.

Particular extracted organic substances such as adhesives may also be sources of constituents which have the capacity to leach out from MDs.

An overview of phthalates that have been identified in MD materials is outlined in Table 1.

Table 1. Identified phthalates in medical device materials[1,2]

Chemical substance	Uses	Harmonised hazard classification[3,4]	ED identification[5]	Rationale for ED designation[6]
dicyclohexyl phthalate [84-61-7]	plasticiser	Reproductive toxin 1B, ED	Confirmed	Phthalate
diisobutyl phthalate:DiBP [84-69-5]	plasticiser	Reproductive toxin 1B, ED	Confirmed	REACH SVHC Phthalate
dibutyl phthalate: DBP [84-74-2, 93952-11-5]	plasticiser	Reproductive toxin 1B, ED	Confirmed	REACH SVHC Phthalate
dihexyl phthalate [84-75-3]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
Benzyl butyl phthalate: BBP [85-68-7]	plasticiser	Reproductive toxin 1B, ED	Confirmed	REACH SVHC Phthalate
bis(2-ethylhexyl) phthalate: di-(2-ethylhexyl) phthalate: DEHP [117-81-7]	plasticiser	Reproductive toxin 1B, ED	Confirmed	REACH SVHC Phthalate, ED
bis(2-methoxyethyl) phthalate [117-82-8]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
di-n-pentyl phthalate: DPP [131-18-0]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
Diisopentylphthalate [605-50-5]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
di-isoctyl phthalate [27554-26-3]	plasticiser	Proposed as Reprotoxin 1B	Suspected	
1,2-benzenedicarboxylic acid: di-C₇₋₁₁-branched and linear alkyl esters [68515-42-4]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear [68515-50-4]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
1,2-benzenedicarboxylic acid: di-C₆₋₈-branched alkyl esters, C₇-rich [71888-89-6]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate
1,2-benzenedicarboxylic acid, dipentyl ester, branched and linear [84777-06-0]	plasticiser	Reproductive toxin 1B	Suspected	REACH SVHC Phthalate

SVHC = A substance of very high concern

[1] In scope of Annex I Section 10.4 of MDR Regulation 2017/745

[2] The presence level is designated in >0.1% of MD materials as having a variable likelihood with some substances being much less prevalent than others

[3] As indicated in Annex VI to CLP_ATP10 (in force from 1 December 2018)

[4] Unless stated otherwise, all reported classifications are harmonised relative to restrictions in some applications

[5] Redetermined as a constituent which presents assumed, suspected or confirmed toxicity according to ISO 10993-17

[6] Based on ECHA's candidate list of substances of very high concern (SVHC) for authorisation according to Article 59(10) of REACH Regulation (EC) 1907/2006 (URL: https://echa.europa.eu/candidate-list-table).

[7] Based on Regulation (EU) 2019/1021 on persistent organic pollutants

The MDR requirements are only applicable to class IIa, IIb and III medical devices, and only when the levels of phthalates present are above 0.1% w/w of the device. Class IIa, IIb and III devices are defined as invasive and which come into direct contact with the human body, or which administer or readminister medicines, body liquids or other substances, or which are involved in the transport or storage of medicines, body fluids or substances.

Ascending inquiry into ED substances in products

The branch of biology and medicine that deals with the hormonal system has evolved rapidly during the 2000's. The rapid growth of the field can be traced to a response to a product used between 1940 and 1971. A synthetic form of oestrogen, diethylstilbestrol (DES) was given to pregnant women to prevent miscarriage and other complications. Effects in daughters exposed to diethylstilbestrol in utero included malformations in their reproductive organs leading to reduced fertility and leaving 1 in 4 of them infertile, as well as a 40 times greater risk of developing cancer of the genital tract and an increased risk of auto-immune diseases. This spurred a marked increase in rigorous scientific work, representing an orderly transition based on theory, testing and synthesis of new ideas. This event, coupled with improved health and occupational regulatory systems, has driven research that aimed to delineate the functioning of the hormonal system and the chemical substances that have the capacity to negatively affect the health of humans. We now recognise the intricate biochemistry of disruption to the hormonal system and its secretions. ED substances can be of synthetic or natural origin, and we can be exposed to them from different sources, such as medicines, residues of insecticides or consumer products that we use in daily life.

In 2001, under the United Nations Environment Programme (UNEP), the UN Environment Chemicals and Health Branch set out to support the implementation of obligations for persistent and semi-persistent organic pollutants under the Basel, Rotterdam, and Stockholm Conventions. The Stockholm Convention entered into force in May 2004. In 2012 the World Health Organization (WHO), together with UNEP, published their 'State of the Science of Endocrine Disrupting Chemicals' (WHO/UNEP, 2012). In 2018, the EU Commission agreed on a comprehensive EU framework on ED substances. This included updating the requirements for data across different legislative frameworks in order to improve the identification of ED substances, and mandating an equivalent approach for the identification and evaluation of ED substances (EC, 2018). Thus, a common consensus for criteria and identification of ED substances was agreed upon across different product categories and different legislative areas, including chemicals, biocides, pesticides, consumer products and MDs. Increased documentation for use of deleterious substances was reflective of this marked development and a greater focus on the development of alternatives was expected.

It is recognised that some phthalates act as ED substances, disturbing the normal function of the hormonal system, with differing and various modes of action. Substances with possible ED activity require in-depth research studies to facilitate understanding of the modes of action. The International Programme on Chemical Safety (IPCS) defined an endocrine-disruptor as follows:

> "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" (IPCS/WHO, 2002).

In November 2018, the European Medicines Agency (EMA) published a revision to its guideline on the environmental risk assessment (ERA) of medicinal products for human use. It indicated growing concern about biologically active pharmaceuticals in the environment. The term 'endocrine active substances' (EAS) was introduced to include all agents that affect development or reproduction. Agents with possible ED activity require tailored testing, which depends on their mode of action (MoA) (EMA, 2018).

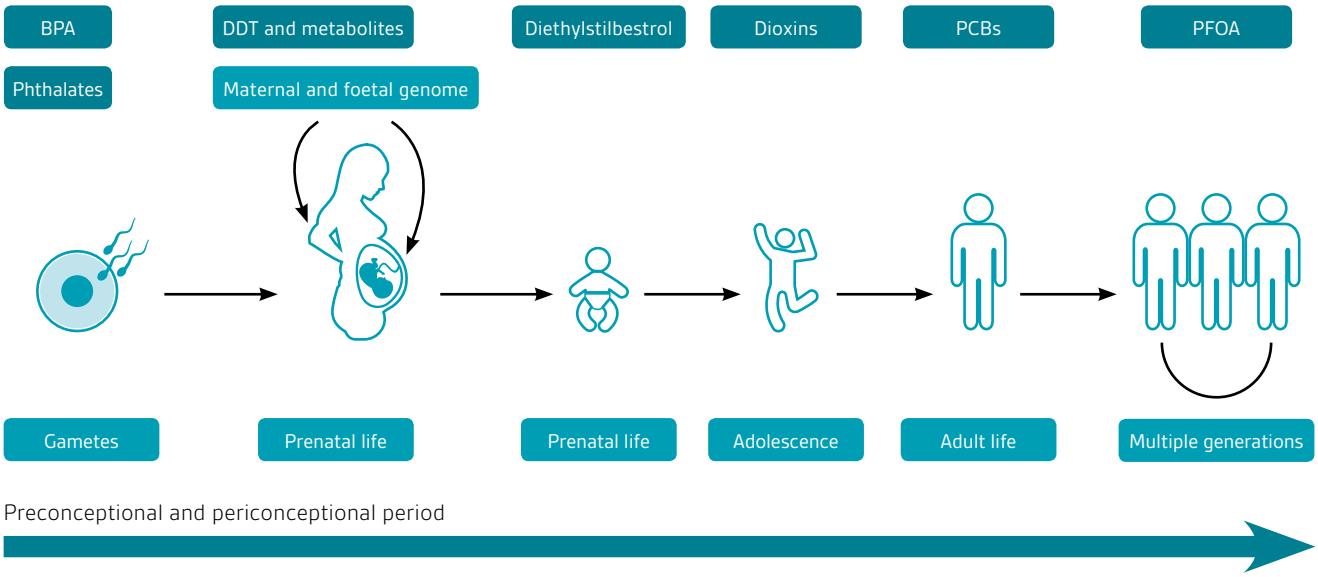
Sensitive periods for ED exposure

Some sub-populations are very sensitive to ED substances. Gestation and early postnatal life (infants and toddlers) are sensitive periods for ED exposure. In particular, the first three months of pregnancy is when all the organs (brain, liver, muscles & skeleton) are formed.

There are now safety concerns identified for the phthalate DEHP for high-risk patient groups such as neonates, infants, pregnant and breast-feeding women, patients undergoing haemodialysis or extracorporeal membrane oxygenation, and prematurely-born infants in Neonatal Intensive Care Units (SCENIHR, 2015).

Clearly, sensitive periods for ED exposure exist (Figure 4). The great majority of nervous system development in children occurs during the first 2 years of life. As a result there are critical periods in developing cognition, sensory and motor faculties during which exposure to an ED substance could be deleterious for specific regions of the brain or other organs and their functions.

Figure 4. The sensitive periods for ED exposure



In 2019, an EU report highlighted the need for further scientific evidence on the extent of exposure and the health effects of ED substances. It concluded that a set of trans-sectorial and harmonized regulations are needed to minimize the human and environmental exposure to ED substances.

Requiring a framework for testing and assessing ED substances is necessary, because the range of possible interactions is so large that they cannot be embodied in one single test. For example, the possible interactions of hormones via the thyroid gland would encompass at least 11 different types of test.

The European Parliament's Committee on Petitions (PETI) and the Policy Department for Citizen's Rights and Constitutional Affairs published a report on 'Endocrine Disruptors: from Scientific Evidence to Human Health Protection' in May 2019. This report confirmed that the definition of ED substances is valid for all sectors. Further test development and validation, such as for disruptors of the 'thyroid axis' is therefore considered necessary (European Parliament, 2019).

Main modes of action of endocrine disruption in toxic responses

When looking for the mode of action of ED substances, the aim is to identify the critical first interaction that can lead to an avalanche of follow-on effects, which result in an effect being seen in the organs or the whole body. Through sufficiently direct binding to a protein in that first interaction, it can affect, block or degrade hormone synthesis and transport in the body. The primary hormone pathways that exist in humans are oestrogen, androgen, thyroid and steroidogenesis, which control a plethora of biological processes such as development, organ balance, metabolism, immune function and reproduction.

It is known that ED substances can act at very low doses with different effects during sensitive periods. As people can be chronically exposed to low doses of multiple contaminants, it is important to identify and gain a clear understanding of the modes of action which underpin the physiological consequences of exposure to clinically-relevant concentrations of ED substances.

ED substances have the capacity to modify the modes of action of hormones by interfering with their metabolism. As some ED substances can alter thyroid physiology at several points, such as synthesis within the thyroid or alteration of clearance mechanisms. These effects can feedback on the growth and function of the thyroid through pituitary function. ED substances can act as direct antithyroid agents, or affect liver-thyroid mechanisms indirectly, or by affecting plasma protein-binding of thyroid proteins, or by interacting with hormones involved in this 'thyroid axis'. This would subsequently change hormone levels in the blood. In adulthood, ED substance exposure has been linked with reduced fertility and thyroid disorders.In some cases, this may increase thyroid hormonal clearance leading to insufficient levels of thyroid hormones in the body creating a negative imbalance. However, it should be noted that the thyroid gland is unique among endocrine organs by virtue of its large storage of hormones and slow overall rate of hormone turnover. It is these features that provide prolonged protection against the depletion of circulating hormone levels should thyroid hormone formation cease. The concurrent tests would therefore be based on the evaluation of alteration of this axis, with thyroid gland histopathology as a primary health conclusion.

Relevant OECD guidance & lines of evidence evaluation

As mentioned earlier, the assessment depends on the MoA of the substance. For this, a tiered testing strategy should be followed (EMA, 2018).

Table 2 below summarises the Organisation for Economic Co-operation and Development (OECD) framework for testing and assessing ED substances that may be appropriate and suitable for different modes of action (OECD, 2018). The major modes of action are also outlined.

Table 2. Relevant OECD test guidelines for the detection of endocrine-disruptors

Test Guidelines (TG)[1,2]	Pathway addressed			
	Oestrogen	Androgen	Thyroid	Steroidogenesis
Level 2: In vitro assays providing data about selected endocrine mechanisms/pathways				
TG 493: In Vitro Oestrogen Receptor Binding Assay	✓			
TG 455: In Vitro Oestrogen Receptor Transactivation Assay	✓			
TG 458: In Vitro Androgen Receptor Transactivation Assay		✓		
TG 456: H295R Steroidogenesis Assay	✓	✓		✓

Test Guidelines (TG)[1,2]	Pathway addressed			
	Oestrogen	Androgen	Thyroid	Steroidogenesis
Level 3: In vivo assays providing data about selected endocrine mechanisms/pathways				
TG 440: Uterotrophic Bioassay	✓			
TG 441: Hershberger Bioassay		✓		
TG 229: Fish Short-Term Reproduction Assay	✓	✓		✓
TG 230: 21-Day Fish Assay	✓	✓		✓
TG 231: Amphibian Metamorphosis Assay			✓	
Level 4: In vivo assays providing data on adverse effects on endocrine-relevant endpoints				
TG 407: Repeated Dose 28-Day Oral Toxicity Study			✓	✓
TG 408: Repeated Dose 90-Day Oral Toxicity Study	✓	✓	✓	✓
TG 421 and 422: Combined 28-Day Reproductive Screening Tests	✓	✓	✓	✓
TG 414: Prenatal Developmental Toxicity Study	✓	✓	✓	✓
TG 426: Developmental Neurotoxicity Study	✓	✓	✓	✓
TG 451-3: Combined Chronic Toxicity/Carcinogenicity Studies	✓	✓	✓	✓
TG 234: Fish Sexual Development Test	✓	✓		✓
TG 241: Larval Amphibian Growth and Development Assay			✓	
Level 5: In vivo assays providing more comprehensive data on adverse effects on endocrine-relevant endpoints over more extensive parts of the life cycle of the organism				
TG 443: Extended One-Generation Reproductive Toxicity Study	✓	✓	✓	✓
TG 240: Medaka Extended One-Generation Reproductive Toxicity Study	✓	✓	✓	✓
TG 416: Two-Generation Reproduction Toxicity Study	✓	✓	✓	✓

OECD = Organisation for Economic Co-operation and Development; EMA = European Medicines Agency
Ref: Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption (OECD 2018)
[1] Embodies mammalian and non-mammalian toxicological studies
[2] Level 1 constitutes existing data and non-testing information

Some initial sources of existing or derived information on ED substances can be found on the International Chemical Secretariat's Substitute It Now List (SIN List), the Endocrine-Disruption Exchange (TEDX) List, the US EPA Endocrine Disruptor Screening Program (EDSP) and the California Proposition 65 List (US EPA, 2009; California Proposition 65 List). It is essential to make use of endocrine-disruptor (ED) assessment lists, regulations related to risk management of chemicals, other sources of information, and to follow practical guidance and assessments in order to identify and designate the phthalates and other individual substances as ED substances.

Selected Regulations Designating ED Substances

Utilising regulations related to risk management of chemicals in Europe

The EU regulations related to the risk management of chemicals in which provisions are made for ED substances can be found in Table 3.

Table 3. Summary of provisions for endocrine-disruptors within these pieces of legislation

Legal Reference	Specific provisions
REACH Regulation (EC) 1907/2006	Endocrine-disruptors are identified: • on a case-by-case basis as substances of very high concern (SVHCs) (Article 57f) • when there is an equivalent level of concern to CMR category 1A or 1B (Carcinogenic, Mutagenic or Toxic to Reproduction) or PBT/vPvB (Persistent, Bioaccumulative & Toxic/Very Persistent & Very Bioaccumulative) substances • based on the definition of the WHO/IPCS NB: There is no definitive guidance for evaluation of endocrine-disrupting potential under REACH
Plant Protection Products Regulation (EC) 1107/2009	An active substance, safener or synergist shall only be approved if based on the assessment: • it is not considered to have endocrine-disrupting properties that may cause adverse effect in humans/ non-target organisms • unless the exposure to that active substance in a product, under realistic proposed conditions of use, is negligible
Biocidal Products Regulation (EU) 528/2012	The following active substances shall not be approved: • those considered as having endocrine-disrupting properties that may cause adverse effects in humans • or which are identified in accordance with Articles 57(f) and 59(1) of REACH Regulation (EC) 1907/2006 as having ED properties
Medical Devices Regulation 2017/745 (MDR)	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, to be (re)administered to the body • shall only contain the following substances in a concentration that is above 0.1 % weight by weight (w/w) where justified pursuant to Section 10.4.2: • substances having ED properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of REACH Regulation (EC) 1907/2006 or, • pursuant to the 1st subparagraph of Article 5(3) of Biocidal Products Regulation (EU) 528/2012 [in accordance with the criteria that are relevant to human health amongst the criteria established therein]

WHO/IPCS = The International Programme on Chemical Safety (IPCS) – World Health Organization
Ref: Grignard, Håkansson and Munn. Reproductive Toxicology 93 (2020) 250-258

The new regulatory requirements contained within the MDR relate both to the safety of these different products and to the general safety and performance requirements (GSPR) for MDs, including the ways in which to designate the phthalates and other substances as ED substances in MDs for achieving product safety.

Designating substances as ED substances

ED substances are designated as such by regulatory measures. Scientific evidence for endocrine-disruption can be difficult to establish even when extrapolation from in vitro cell responses and in vivo animal studies are performed to determine human effects.

The guidance related to designating substances as ED substances and their identification is shown in Table 4.

Table 4. Scientific assessment criteria for the determination of endocrine-disrupting potential

Legal reference	Assessment criteria	Basis
Commission Delegated Regulation (EU) 2017/2100 [September 2017] setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) 528/2012 Commission Regulation (EU) 2018/605 [April 2018] amending Annex II to Regulation (EC) 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties	Substances are considered as having ED properties that may cause adverse effects in humans if it meets all the following criteria: • 'it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences; • It has an ED mode of action [one that alters the function(s) of the endocrine system]. • the adverse effect is a consequence of the ED mode of action	Based on: - properties with respect to humans (Section A) - properties with respect to non-target organisms (Section B) - all available relevant scientific data - An assessment of this data based on a weight-of-evidence (WoE) approach to establish whether the criteria are fulfilled - link between the adverse effect(s) and the ED mode of action is biologically plausible
CLP Regulation (EC) 1272/2008 [December 2008] on classification, labelling & packaging of substances & mixtures (amending and repealing Directives 67/548/EEC & 1999/45/EC, & amending Regulation (EC) 1907/2006)	• CMR Category 1A: Known to be a human carcinogen, mutagen or reproductive toxin[1]	Based on evidence from humans
	• CMR Category 1B: Presumed to be a human carcinogen, mutagen or reproductive toxin[1]	Based on studies in animals
	• CMR Category 2: Considered to be a suspected carcinogen, mutagen or reproductive toxin[1]	Based on limited evidence from studies in animals or clinical manifestations from people

CLP = Classification, Labelling & Packaging (CLP) Regulation (EC) 1272/2008; Based on the United Nations' Globally Harmonized System (GHS); CMR = Carcinogenic, Mutagenic or Toxic to Reproduction

[1] The classifications are reconciled via harmonized classification and labelling (CLH) in Europe

The most concise identification of ED substances is as Carcinogenic, Mutagenic or Toxic to Reproduction (CMR). There is also a link between the ED mode of action and the adverse effect(s) of a substance with possible ED activity. Therefore, according to the ED criteria, all available data are to be used to provide a clear link between the two in a stepwise weight-of-evidence (WoE) approach.

In the MDR there is a special restriction for the use of both CMR and ED substances.

If the substance is considered to have ED properties, for example, using ECHA's endocrine-disruptor (ED) assessment list, then confirmation through the decision-making processes and formal risk management under REACH/BPR is needed before any regulatory action can be taken.

Practical guidance and further assessments and investigations are provided here to assist in identifying substances as having possible ED activity can be found in Table 5.

Table 5 Practical guidance & assessments for the identification of endocrine-disruptors

Legal reference	Assessment strategy	Source
SVHC REACH candidate list of substances of very high concern for potential inclusion in REACH Annex XIV.	• on a case-by-case basis as substances of very high concern (SVHCs) (Article 57f) • ED properties with probable serious effects to humans	REACH Annex XIV; ECHA, 2006; ECHA, 2021
Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling & packaging (CLP) of substances & mixtures. [Version 5.0. July 2017]	• when there is an equivalent level of concern to CMR category 1A or 1B; • or PBT/vPvB substances	Regulation (EC) No 1272/2008; ECHA, 2017
EFSA/ECHA guidance for the identification of endocrine-disruptors in the context of Regulations (EU) 528/2012 and (EC) 1107/2009	Involves: • Information gathering • Evidence assessment • Initial analysis of evidence • Mode of action (MoA) analysis1 • ED criteria conclusion	EFSA/ECHA, 2018
ECHA's endocrine-disruptor (ED) assessment list	Involves: • substances with potential ED activity • substances undergoing an ED assessment under REACH or the Biocidal Products Regulation • substances for which hazard assessment for ED potential is either ongoing or completed since the start of the implementation of the SVHC Roadmap in February 2013	https://echa.europa.eu/ed.assessment ECHA, 2021

SVHC = A substance of very high concern; ECHA = European Chemicals Agency; EFSA = European Food Safety Authority

NB: It is worth noting that a substance that holds an ED mode of action is one which is biologically substantiated (and not only inferred).

As can be seen above, ECHA's database on chemical substances is the most up-to-date, key source of information on individual substances. Also, the EFSA/ECHA guidance is very useful if one would like to establish substances with endocrine disrupting properties regardless of their intended application (Boberg et al., 2020). Following this, a tailored risk assessment will therefore be necessary, including of possible ED activity.

If a substance is identified as having possible ED activity, there are then specific provisions that the MDR sets out for medical devices that must be met for their safety and performance, with specific requirements regarding design and manufacture.

Specific safety & performance requirements in the MDR

These safety & performance requirements are related to the specifications regarding CMR/ED substances and can be compared with the former essential requirements (ER 7.5) of the Medical Devices Directive 93/42/EEC (MDD) as shown in Table 6.

Table 6. Former requirements (Medical Devices Directive 93/42/EEC (MDD))

Provision	Comparison with the MDR	Implication
7. Chemical, physical & biological properties		
7.5. Essential Requirements		
	[Comparable to 10.4.1. Design & manufacture of devices]	– Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction NB: No requirements for justification or labelling of toxic substances other than phthalates
	[Comparable to 10.4.2. Justification regarding the presence of CMR &/or ED substances]	– Risk-based justification generally accepted for highly toxic substances consistent with ISO 14971 and MDD – All risks should be reduced to the lowest level practicable, bearing in mind the generally acknowledged state of the art, the benefits to the patient and the practicability of further risk reduction [consistent with ISO/TR 24971:2020 Annex C3]
	[Comparable to 10.4.3. Guidelines on phthalates]	Not present
	[Comparable to 10.4.4. Guidelines on other CMR & ED substances]	Not present
	[Comparable to 10.4.5. Labelling]	
If parts of a device… [that are invasive or administer substances] contain phthalates classified as [CMR]		– these devices must be labelled… as a device containing phthalates
If intended use of devices containing [phthalates] includes [vulnerable populations]		– a specific justification for the use of [phthalates] with regards to compliance with the essential requirements – information on residual risks for vulnerable populations and appropriate precautionary measures in the IFU

MDR = Medical Devices Regulation 2017/745

Table 7 lists the specific safety & performance requirements of MDs in the Medical Devices Regulation 2017/745 (MDR)

Table 7. New requirements for medical devices under the Medical Devices Regulation 2017/745

Special provision	Implication
10.4. Substances	
10.4.1. Design & manufacture of devices[1]	
Devices / parts / materials that: • are invasive and which come into direct contact with the human body • (re)administer medicines, body liquids or other substances • transport or store medicines, body fluids or substances	– shall only contain [CMR substances & ED substances] in a concentration above 0.1% (w/w) when justified – (labelling & justification requirements apply)
10.4.2. Justification regarding the presence of CMR &/or ED substances[2]	
Justification for the presence of such substances [CMR 1A or 1B or endocrine-disrupting chemicals] in a medical device above 0.1% (w/w)	Justification for the presence of CMR 1A or 1B or ED substances above 0.1% (w/w) shall be based on: – (a) an analysis (and estimate) of potential patient and user exposure to the substance – (b) an analysis of the possible substitute substances (including available research) – (c) justification in relation to functionality, performance and benefit-risk ratio (including use in susceptible groups) – (d) most recent scientific committee guidelines on the benefit-risk assessment of the presence of such substances
10.4.2. Justification regarding the presence of CMR &/or ED substances[2]	
Phthalates guidelines	– Requires relevant scientific committee to embody a benefit/risk analysis (BRA) (EMA, 2014; SCHEER, 2019) – Justification: Benefit-Risk Analysis (BRA) accounts for the intended purpose and context of the use of the device, as well as any available alternative substances and materials, designs or medical treatments
10.4.4. Guidelines on other CMR & ED substances	
CMR and ED substances guidelines	– Identifies substances that are carcinogenic, mutagenic or toxic to reproduction (including endocrine disruptors), Category 1A or 1B (CLP Regulation 1272/2008; Annex VI, Part 3) – When needed guidelines are to be drafted as those for benefit/risk analysis (BRA) and use of CMR/ED phthalates [The phthalates guidance includes a statement that the phthalates guidance can be applied other CMR/ED substances. Therefore, in the absence of a guidance document from SCHEER for other CMR/ED substances, the phthalates guidance can be applied] – Justification: Requires a case-by-case assessment and may require identification
10.4.5. Labelling	
Where devices, parts thereof or materials used therein [that are invasive or administer substances] contain [CMR/ED substances above 0.1% w/w]	– the presence of those substances shall be labelled… with the list of such substances
If intended use of devices containing CMR/ED substances includes [vulnerable populations]:	– justification for CMR substances covered by 10.4.2. – information on residual risks and precautionary measures shall be given in the IFU

[1] This requirement is only applicable to certain medical devices
[2] This requirement is only applicable when CMR & ED substances are at levels >0.1%
GSPR = general safety and performance requirements; IFU = instructions for use; vulnerable populations = children, pregnant or breastfeeding women and other susceptible patient groups

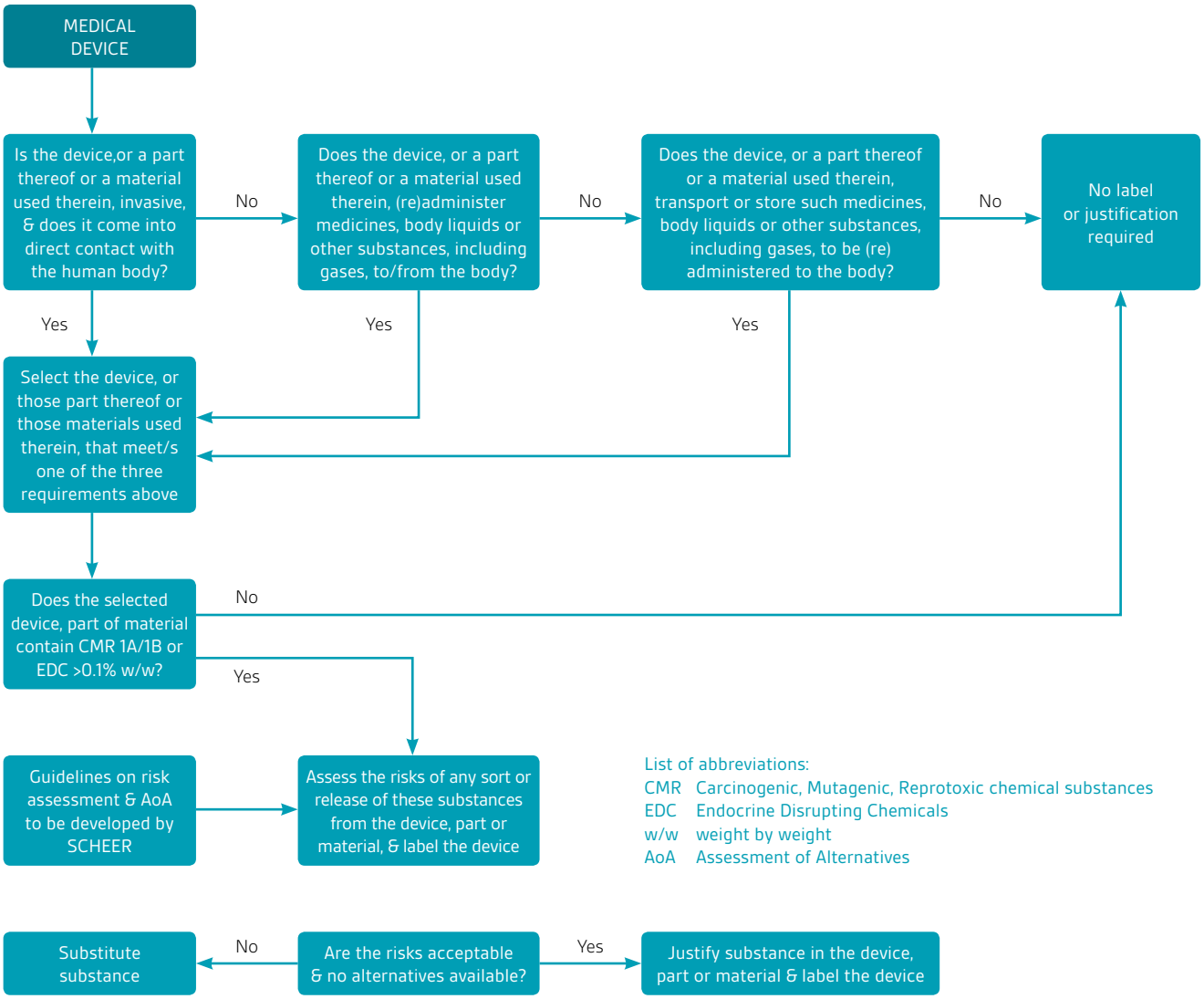
It is important to note that according to the MDR Section 10.4.1. (Design and manufacture of devices), this section is exclusively concerned with presence of CMR substances and ED substances in medical devices at a limit above <0.1%. If CMR 1A, CMR 1B or ED substances are found above 0.1% (w/w), a formal justification is required. Thus, manufacturers have obligations to provide justification and appropriate labelling if certain types of MDs contain more than 0.1% (w/w) of substances classified as CMR 1A or 1B or have endocrine-disrupting (ED) properties.

Overall Nonclinical Assessment of Phthalates in Devices

Nonclinical assessment of CMR 1A/1B & ED substances in medical devices

For toxicological testing of ED substances, the OECD framework for testing and assessing ED substances is referred to in an earlier section (see relevant OECD guidance and lines of evidence evaluation). As there are over 1200 substances that hold CLP classification of CMR 1A or 1B, justifications and labelling are therefore required for many medical devices. It follows that safety evaluations are therefore required during the development or manufacture of a product and for an existing marketed product.

Figure 5. Scope of the MDR Section 10.4 for CMR 1A/1B substances and ED substances



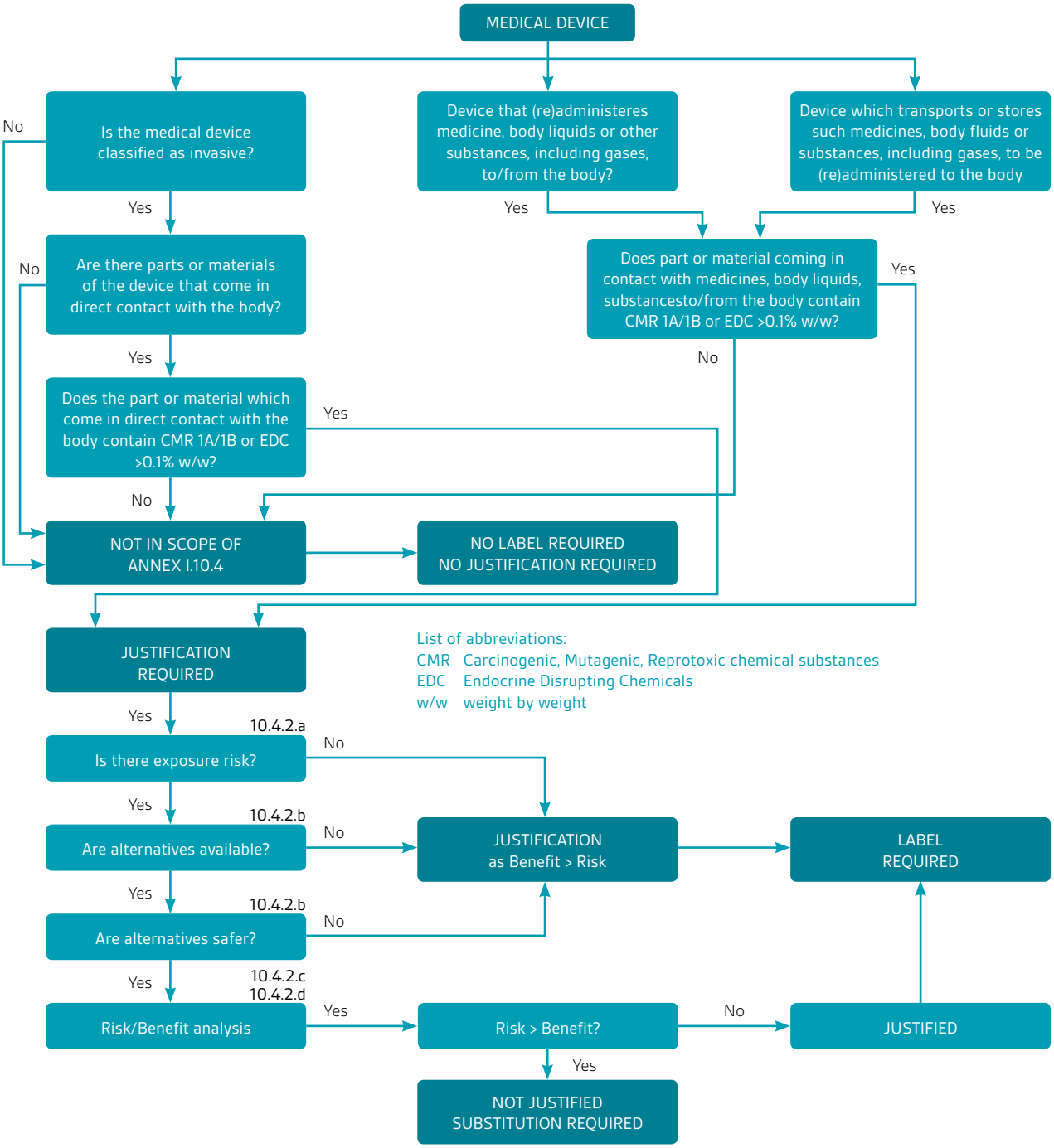
Post-market surveillance involves changes in clinical usages and changes to reagents, residual solvents, routes of synthesis or process conditions and changes to formulation (limited to new impurities or those CMR 1A/1B substances and ED substances that have increased amounts). This is particularly important when there are changes to the clinical use of the product, such as an increase in its duration of use, new routes of administration or new patient subpopulations that may impact the previous assessments; or when new data indicate an existing impurity holds a CMR or ED classification, or when a new CMR or ED impurity is suspected.

Therefore, limits of these substances must also demonstrate 'As Far As Possible' in the MDR and 'As Low As Reasonably Practicable' (ALARP) or 'As Low As Reasonably Achievable' (ALARA) principles underpinned by the Failure Mode and Effects Analysis standard. These indicate process control and safety have been carried out to a reasonable degree, and that reducing the risk further would be grossly disproportionate to the benefit gained. These limits may be larger in early clinical development and should be re-assessed at each stage.

If these limits were determined based on the limits of safety, and not based upon manufacturing experience, the rationale for this determination should be explained. If the impurity cannot be reduced below 0.1% (w/w) and the levels are minimal and the risk is reduced 'as far as possible', a higher level may be justified based on a benefit/risk analysis (BRA). Accordingly, the level is expected to be well within that which is evaluated as safe and tolerable for the patient. Overall, slight-to-moderate risks might be acceptable when these are outweighed by the benefits to the patient.

Figure 6 below outlines the flow process for the nonclinical assessment of CMR 1A/1B and ED substances that may be found in MDs.

Figure 6. Overall nonclinical assessment of CMR 1A/1B & ED substances in medical devices



Implementation of the standards ISO 14971, ISO 10993-1 and ISO 10993-17 is supported by the fact that exposure to these substances as intentionally-added constituents in MDs can be found and determined to be greater than their internal exposure and clinically-relevant health effects. Phthalates can be therefore reaffirmed as suitable, when based in part on their absorption, intrinsic toxicity, clearance in humans, and the safety margins between conservative estimates of internal exposure and their lack of significant deleterious or pernicious potential.

Exposure & dose

A patient's risk of an adverse health effect is determined by evaluating external exposures (contacts) and internal doses (entry to the body). The concept of dose is therefore different from exposure. In this context, 'exposure' is the chance for the body to have contact with and then absorb a foreign chemical. This implies that the foreign chemical is in some physical proximity to the patient.

For a patient to receive a dose of a substance, clearly, an exposure must occur first. Following this first contact, we refer to dose or dosage. In contrast, dose is not only about the contact, 'dose' implies that an actual amount of the chemical is absorbed by the patient.

Consequently, the external exposure varies considerably according to its source. It therefore follows that the further the patient is from the source of the chemicals, the lower their exposure and the less likely it would be for a patient to receive an internal dose.

An exception to this can be seen with respiratory equipment and fluid pumps, including the tubing applied. Even when different patients have similar exposure patterns, the actual dose received will depend on several different clinical considerations regarding utility.

If exposure from the MD is below a recognized threshold, the hazardous situation is expected to still exist, however, the probability of it occurring becomes low and the risk is considered to be reduced 'as far as possible'.

The factors that moderate exposure include the size and configuration of the MD, the intended purpose and context of the use of the MD, the exposure pattern (for example, duration of contact, frequency, co-exposure, and timings of withdrawal). The maximum dose a patient could be exposed is then calculated under intended use of the MD in its clinical conditions.

Exposure assessments are therefore required for the risk assessment to determine if there is a risk and whether the constituents would elicit potential effects if in the blood of patients.

Deriving safety margins for particular health conclusions

Measurable outcomes resulting in a conclusion of toxicological concern may be a biochemical or pathological effect which exhibits percentage or proportional change. Thus, the dose-response relationship is graded between a level which has no effect, and one at which maximal effect is demonstrated. The dose-response relationship is predicted based on 'cause-and-effect' considerations. Investigation into doses at which health effects may not be elicited and would not be expected to occur leads to the process of establishing tolerable intakes (TI) for the identified constituents.

The tolerable intake values protect human health from harm due to constituents that might leach from MDs.

These tolerable intake values for selected phthalate esters are summarized in Table 8.

Table 8. Tolerable intake of selected phthalate esters

Phthalate	Critical effect	Risk assessment[1] (Pod/MF)	Tolerable intake (TI)[4,5]	EFSA Tolerable Daily Intake (TDI) values
Diisobutyl phthalate (DiBP)	Decreased foetal testosterone production $BMDL_{1SD}$ = 80 mg/kg-day LOAEL = 300 mg/kg-day	$BMDL^{1SD}/100$[2]	0.8 mg/kg-day or 0.00288 mmol/kg-day	0.15 mg/kg-day
Dibutyl phthalate (DBP)	Decreased foetal testosterone No-observed-adverse-effect level = 30 mg/kg-day LOAEL = 50 mg/kg-day	NOAEL/100	0.3 mg/kg-day or 0.00108 mmol/kg-day	0.01 mg/kg-day

Phthalate	Critical effect	Risk assessment[1] (Pod/MF)	Tolerable intake (TI)[4,5]	EFSA Tolerable Daily Intake (TDI) values
Benzyl butyl phthalate (BBP)	Decreased foetal testosterone production $BMDL_{1SD}$ = 102 mg/kg-day LOAEL = 300 mg/kg-day	$BMDL_{1SD}/100^{2}$	1 mg/kg-day or 0.00327 mmol/kg-day	0.5 mg/kg-day
Diethylhexyl phthalate (DEHP)	Small or absent male reproductive organs $BMDL_{10}$ = 27 mg/kg-day LOAEL = 14-23 mg/kg-day	$BMDL_{10}/100^{3}$	0.3 mg/kg-day or 0.000692 mmol/kg-day	0.05 mg/kg-day [SCENIHR, 2015]
Dipentyl phthalate (DPP)	Decreased foetal testosterone production $BMDL_{1SD}$ = 17 mg/kg-day LOAEL = 100 mg/kg-day	$BMDL_{1SD}/100^{2}$	0.2 mg/kg-day or 0.000548 mmol/kg-day	-
Diisononyl phthalate (DiNP)	Decreased foetal testosterone LOAEL = 750 mg/kg-day	LOAEL/1000	0.8 mg/kg-day or 0.00179 mmol/kg-day	0.15 mg/kg-day

[1] PoD is the point of departure and MF is the total modifying factor to account for uncertainty
[2] $BMDL_{1SD}$ = lower 95% confidence limit of the exposure required to induce a 1 standard deviation decrease in testosterone
[3] $BMDL_{10}$ = lower 95% confidence limit of the exposure required to induce a 10% increase in adverse effect
[4] The tolerable intake (TI) in mg/kg-day is rounded to one significant digit
[5] Tolerable intake (TI) (mmol/kg-day) = TI (mg/kg-day)/molecular weight (mg/mmol)

From these TI values that we have derived above, it is possible to derive margins of safety (MOS) to protect human health. This tolerable intake is intended to protect people from any of the adverse effects that might occur during neonatal or adult life, and at a much higher exposure. Large differences in exposure (measured in mg/day or kg/day) are not anticipated in the general population (EC, 2017; EFSA, 2019). There are also several studies on how to calculate the synergistic exposure of more than one chemical, considering also low doses (Miraculix Project, 2020).

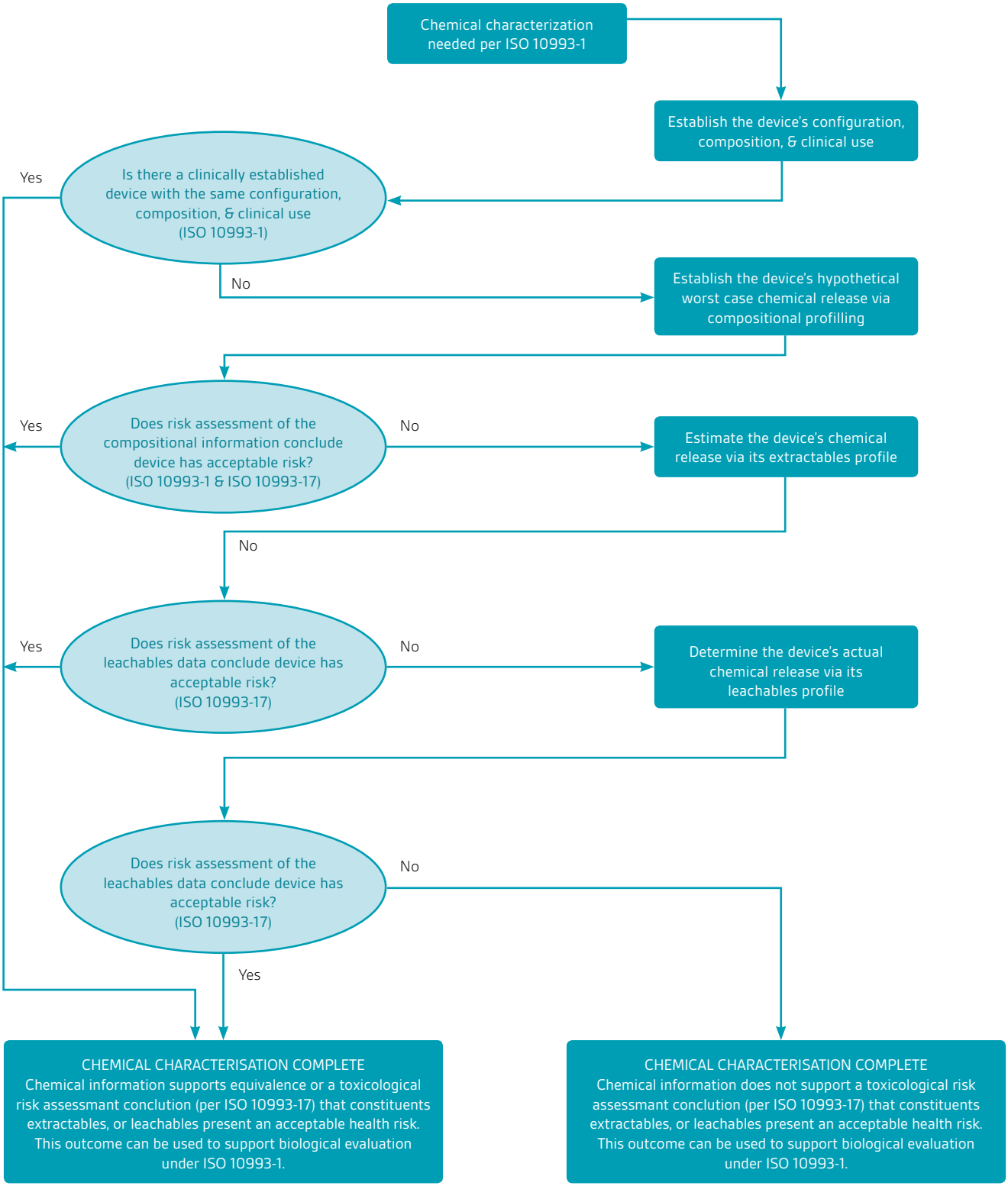
Chemical characterisation as per BS EN ISO 10993-18 and BS EN ISO 14971

Clearly, the characterisation of chemicals in an MD, its components or its materials of construction involves multiple processes, including information gathering and generation. Chemical characterisation is the process of obtaining chemical information about an MD, prior and relevant to its biological evaluation and any toxicological risk assessment. One of the challenges in this process is to make a direct comparison between the predicted external exposure based on compositional levels within the product and its configuration and formation. Thus, clarity is needed for the MD innovator with respect to:

— establishing the MD's material composition and configuration

— identifying and quantifying extractables and leachables linked with the MD

Figure 7. Chemical characterization process



The proposed mechanisms of interaction and monitoring of impact of the leachables on the product on a routine basis provides further clarity. Therefore, there is the need to balance product safety and quality during development and throughout the lifecycle management of MDs. It is essential to develop a scientifically robust comparison of MD configuration based on absolute (observed) exposures, concentrations or amounts. For manufacturers, the burden of proof is further improved and optimised with careful risk management of an MD throughout its lifecycle.

Extractables & leachables profiling

It is therefore recommended that extraction studies qualify and quantitate the profile of extractables from components and materials in MDs using a combination of multiple extraction techniques. It would therefore be possible to envisage several potential applications:

- Identifying and quantifying the additives or ingredients in a material to forecast extractables
- Identifying extractables to forecast leachables in specific dosage forms
- Exercising quality control over incoming materials in a system

In studies of extractables and leachables, analytical methods are designed for screening samples for unspecified analytes, and for testing samples for specified (targeted) analytes. Selecting an extractable as a target leachable leads to finding that target leachable in finished product at a measurable level. It is recommended that the conditions of extraction are reflective of the potential contact with the MD.

Deriving & applying the analytical evaluation threshold (AET)

When an extractable has been detected it is necessary to consider the safety impact that extractable might have as a leachable. However, if the extractable's identity cannot be established, a toxicological risk assessment of this extractable, as described in BS EN ISO 10993-17, cannot be performed. Furthermore, if the extractable is inaccurately quantified, the outcome of any toxicological risk assessment may be incorrect. To ensure accurate quantification and establish that the analytical method is suitable for its intended use, the 'limit of qualification/ limit of detection' is applied, where the lowest quantity of a substance is distinguished from the absence of that substance with a stated confidence level.

The application of the threshold concept facilitates extractables assessment decisions based on the concentration of the extractable in an extract. The Analytical Evaluation Threshold (AET) enables the analytical chemist to address the question of whether a specific extractable need be identified and quantified for toxicological risk assessment.

Table 9. Case Example of Determination of the Analytical Evaluation Threshold (AET)

Contact category	Number of devices that were extracted to generate the extract	Volume of the extract (ml)	Clinical exposure (under normal clinical practice) (number of devices/day)	Dose-Based Threshold (DBT) (µg/day)	Uncertainty Factor (UF)	Analytical Evaluation Threshold (AET) (µg/ml)
Limited contact[1]	1	9.0	1	120	2	6.6
Prolonged contact	4	100	2	120	1	2.4
Long-term contact[2]	20	33.3	1	120	2	18.0
Long-term contact[2]	20	33.3	1	0.75[3]	2	0.23

[1] A limited contact MD such as a treatment for shingles
[2] A permanently implanted MD such as a cardiovascular pacemaker
[3] If the actual release kinetics of leachables establishes that the exposure to extractables is less than 10 years, then the kinetic data can potentially support a higher DBT value (see PD ISO/TS 21726)

If the determined specific extractable or targeted leachable level is:

– BELOW the AET level (Specific Dose < AET) then further information will not be needed to support safety of the constituent. Further work on this individual extractable or targeted leachable is not necessary. This AET level can then be tied to the threshold of toxicological concern (TTC) to reveal levels of safety for unidentified compounds, or the qualification threshold (QT) below which a given noncarcinogenic leachable is not considered for safety qualification (e.g. by toxicological assessments) unless the leachable presents a structural–activity relationship, or the safety concern threshold (SCT), a value below which leachables are not considered for identification and toxicological qualification.

– ABOVE or EQUAL to the AET level in the MD material being tested (Specific Dose ≥ AET), then this constitutes an exposure that may require this constituent to be fully identified and quantified, and then assessed for toxicological risk. Further work to determine the potential risks attributable to the individual extractable or targeted leachable may then be assessed according to BS EN ISO 10993-17.

The proposed Specific Dose ≥ AET as evidence of the clinical usage of the constituent provides a strong argument for the biological assessment of this constituent based on exposure data. This approach is also robust, as a Specific Dose ≥ AET outcome would be investigated further by careful assessment of all biological data, which would then support the configuration of MDs for manufacturers.

Implications for the Future Use of Phthalates

When considering the limitations and uncertainties, there are several implications for the future reassessment and use of modern phthalates.

Clearly, when considering their substitutes, the post-submission approval involves changes to routes of synthesis, reagents, residual solvents or process conditions and changes to formulation. Although this tends to be limited to new impurities or those with increased amounts, we also therefore consider the implications for the future reassessment and use of phthalates and their substitutes.

Evolving safety assessments

The identification of possible alternatives is profoundly affected by the following factors in Table 10.

Table 10. Factors influencing evaluation of constituents (SCHEER, 2019)

Factor	Example[1]
Identification of substances/ material	DEHP has stabilising effects on red blood cells (RBCs). Leads to a prolonged shelf-life and higher RBC survival
High functionality	Phthalates impart flexibility into tubing required for their intended clinical use
Clinical benefit	Blood bag materials – improves resistance to heat and other chemicals (in particular, during sterilisation). Ensures stability of pH and oxygen levels
Material benefit	Current new chemical plasticisers recently added to the European Pharmacopoeia: • Hexamoll® DINCH (cyclohexane 1,2-dicarboxylic acid, diisononyl ester) • BTHC (butyryl tri-n-hexyl citrate) • TOTM (tris(2-ethylhexyl) trimellitate) • DEHT (bis(2-ethylhexyl) terephthalate) Ideal for different containers for human blood and blood components including tubing. High flexibility and low release potential
Concentration level (% w/w)	For reasons of safety, the maximal level of extractable DEHP is set at 15 mg/100 mL of blood (see BS EN ISO 3826-1)

Factor	Example[1]
Leaching from MD under relevant conditions (mg/hour-day)	Data on the nature and duration of contact, population exposed, and maximum number of MDs used by a patient in one day can be obtained during the clinical use of the MD. Such clinical exposure data can be obtained from human biological fluids/tissues for MDs that directly contact the body, and clinical non-biological fluids such as saline for MDs that indirectly contact the body
Exposure estimation for relevant route of exposure	Quantitative results such as the descriptions of internal dose and estimated external exposures. Estimated daily exposure (EDE) may be adjusted to account for low frequency or intermittent use (or contact). Time-averaging considered in cases where leachability is expected to continue for the long-term
Intrinsic hazard identification	Investigation of health endpoints other than reproduction, such as effects on the immune system and metabolism, together with ED properties (e.g. repeat-dose toxicity, organ toxicity, CMR properties and biological compatibility)
Risk characterisation	Elicitation, logical soundness, uncertainty and selection of an ED substance in MDs. Leads to inspection of the problem, objectives, alternatives, consequences, trade-offs, uncertainty, risk tolerance and linked decisions
Technical feasibility	Substances (with possible ED activity) are used for specific purposes depending on the intended use of the MD. The more suitable the characteristics of the substance to be introduced, the greater the optimal flexibility to the device it provides. Reason: the ability of phthalates to decrease the viscosity of vinyl materials in the device and subsequent improvement of flexibility. Fine tuning of flexibility of phthalates is an excellent example of the importance of optimal flexibility without kinking in the clinical utility of a PVC-based MD

[1] Techniques for differentiating between MD constituents include Benchmark dose (BMD) analysis, Multicriteria decision (MCDA) analysis, in silico analysis (such as Danish EPA VEGA-QSAR) and PBPK modelling.

Clearly, for a new or modified medical device the materials of construction and manufacturing should not introduce chemicals that raise concern, as it will simply be compared with an already marketed device which is safe and compatible together with its identical intended clinical usage.

Accordingly, the use of CMR/ED substances is restricted to uses below 0.1% w/w in a MD according to the MDR. On a case-by-case basis, clinical experts will reach conclusions on the benefit of the presence of CMR/ED phthalates regarding the device's intended usage and exposed patient-group, balanced with clinically relevant differences.

An integral part of product safety and standards, the factors described in Table 10 by the Scientific Committee on Health, Environmental and Emerging Risks, including the clinical performance of the intrinsic materials, are expected to be evaluated for every component in a MD that contains CMR/ED phthalates above the 0.1% w/w level (SCHEER, 2019).

For example, if a patient in early adulthood were to be undergoing an acute type-1 anaphylaxis; a sudden, potentially severe and life-threatening allergic reaction, antihistamines such as diphenhydramine and histamine-2 blockers such as cimetidine or famotidine would be given intravenously until the symptoms were to disappear. If breathing were to be severely impaired, a breathing tube may be inserted into the trachea through the mouth and oxygen would be given through the breathing tube if required. Ensuring stability of oxygen levels, maintaining supportive measures, and actively mastering the flexibility of tubing for breathing to keep the patient alive in the hospital would clearly counterbalance the risk of exposing the patient to a slightly elevated level (above 0.1% w/w) of a substance (with possible ED activity) for the limited duration of contact (for less than 24 hours).

Modifications in the design of MDs and clinical procedures such as process, technique or treatment modification, or replacements with chemical substitutes are factors imperative for the selection of plasticizers and waterproofing agents. Identifying the right substitutes and the criteria that differentiate them are important factors implicating their future use.

Conclusion

The utilisation of the right phthalate or a valid substitute together with reformulation of particular excipients to lower concentration preparations may be the most suitable advancement.

- On balance, it appears that many substances with possible ED activity (Table 1 – 2), do not cause significant adverse effects on glandular function in the clinic. However, phthalates that produce glandular alterations in animals are used to impart flexibility to plastics in clinical practice which are themselves linked with alterations to glandular function.
- The precise relationship between phthalate and glandular function therefore requires careful delineation of the related changes and clinical studies that permit evaluation of reproductive risk in humans. There is also limited evidence that exposure to some phthalates which deplete circulating hormone levels may pose some risk of synergy with other specific chemicals with possible ED activity.
- Substances including phthalates are designated as ED substances according to the specific definitions in different regulations, and an elevated focus on chemicals with these properties points towards a set of internationally agreed regulations from different sectors for which the ED definition is valid across all sectors.
- From the definition of the WHO/IPCS and OECD to the designation as CMR substances by ECHA under the CLP Regulation (EC) 1271/2008 (Table 4 – 5), the EFSA/ECHA guidance and the Substances of Very High Concern (SVHC) REACH candidate list are used in furtherance of the identification of ED substances. Phthalates can thus be determined to be reproductive toxins 1B or SVHCs under REACH. Identifying EDs is an ongoing process and always in motion. However, the regulation of substances with possible ED activity depends upon the use of that individual substance rather than its intrinsic properties.
- As we aim to avoid unexpected toxicity to occur from clinical procedures, safety evaluations are therefore required during the development or manufacture of a product as well as for existing marketed products. The general structure of the current framework and ED designation does appear to be consistent with the CMR criteria for Reprotoxin 1B. However, it is important to follow new updates under the surrounding need for a body of evidence on the investigations of risk.

- When it comes to circumstances of the potential disruption to the hormonal and reproductive system there are still cases presenting diagnostic challenges, and those with scientific evidence that remain difficult to establish, where some agents would surely still have to be discovered as having potential ED activity. The ECHA/EFSA guidance for other types of substances can be effectively utilized to facilitate this discovery and bring an assessor to a conclusion as to a chemical's ED status.
- Encircled by five new provisions in the MDR 2017/745 (Annex I GSPR 10.4) (Table 7), these general safety and performance requirements regulate phthalates, which are currently prohibited at a level above 1%, in MDs. In the general safety and performance requirements (GSPR) in the MDR, specific restrictions for the use of both CMR and ED chemicals hold a special place. The MDR contains provisions not to use CMR/ED phthalates or compounds above 0.1% in MDs, enabling the manufacture of MDs considered safe for clinical practice, and which is also likely to render the potential risk of synergy as minimal or negligible.
- Pivotal to the revitalized focus on phthalates and their substitution, precise investigations give way to clinical exposure dosages in such a way that compositional profiling and Analytical Evaluation Threshold (AET) determinations take shape and become accurate. This achieves an optimal analytical performance at analytical evaluation threshold levels that may be unobtainable in the finished product. This AET level can then be tied to the threshold of toxicological concern (TTC) or the safety concern threshold (SCT), which should elicit higher functionality in analysis and lead to evolving levels of safety for all substances that are present.
- In 2019, SCHEER produced and affirmed special guidelines on the benefit/risk analysis of phthalates in MDs (Table 10). A benefit/risk analysis is required when phthalates exist in an MD. This needs to account for the intended purpose and context of the use of the MD, as well as any available alternative substances and materials, designs or medical treatments. Thus, the techniques in this paper are not implied to be arbitrarily applied; they reflect a rigorous, logical, scientific effort to establish clear profiling of MDs by concisely placing the MDR standards of safety into context as a benefit to manufacturers.
- Combining a broad treatment for assessing the safety/performance balance of a new MD with our collective aim to outline and galvanize recommended optimal practice with sufficient latitude can facilitate material selection.

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