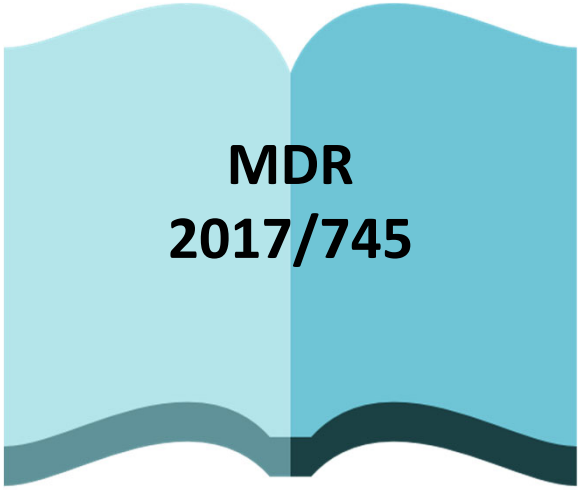
MEDPASS
INTERNATIONAL

Biological Evaluation
for
MDR

AGENDA

- Comparison of relevant GSPRs of the MDR with the ERs of the MDD
- Comparison of relevant GSPRs of the MDR with ISO 10993 & 14971
- Impact of changes in ISO 10993-1:2018 and other ISO standards

Overview



- **Question: What is the impact of the MDR on the biological evaluation of medical devices?**
- **Answer: None!** (assuming you were doing it right!)

(and if you exclude the CMR requirements)

Spoiler Alert!!!

Comparison: GSPRs vs ERs or ISO 14971

MDD ERs 1, 2 & 6

Three of the **general ERs** are relevant to biological safety

General ERs relevant to **risk management** were poorly drafted and resulted in **content deviations** in Annexes Z in EN/ISO 14971:2012

MDR GSPRs 1, 2, 4 & 8

Four of the **general GSPRs** are relevant to biological safety

General GSPRs relevant to **risk management** were aligned with ISO 14971 and thus with **generally accepted risk management principles**

GSPR 2 is new: risk reduction as far as possible without affecting the benefit-risk ratio

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.1

Devices must be designed and manufactured… to guarantee the characteristics and performances referred to in Section I

Particular attention must be paid to:

MDR GSPR 10.1

Devices shall be designed and manufactured … to ensure that the characteristics and performance requirements referred to in Chapter I

Particular attention shall be paid to:

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.1

– the choice of materials used, particularly as regards toxicity and, where appropriate flammability;

– the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device;

ISO 10993-16 addresses ADME

MDR GSPR 10.1

(a) the choice of materials and substances used, particularly as regards toxicity and, where relevant, flammability;

(b) the compatibility between the materials and substances used and biological tissues, cells and body fluids, taking account of the intended purpose of the device and, where relevant, absorption, distribution, metabolism and excretion;

Comparison: GSPRs vs ERs or ISO 10993

ISO 10993-1

Not included in MDD or ISO 10993-1:2018

- Not within scope of biological evaluation

ISO 10993-1: **final product**, subjected to all manufacturing processes, must be evaluated. (Includes all constituents, processing aids, packaging, sterilization, etc.)

MDR GSPR 10.1

(c) the compatibility between the different parts of a device which consists of more than one implantable part;

(d) the impact of processes on material properties;

Comparison: GSPRs vs ERs or ISO 10993

ISO 10993-1

Not included in MDD or ISO 10993-1:2018
- Not within scope of biological evaluation, except as part of material characterization

ISO 10993-1 &19: evaluation of physical characteristics required

ISO 10993-1: physical and chemical characterization shall precede any biological testing

MDR GSPR 10.1

(f) the **mechanical properties** of the materials used, reflecting, where appropriate, matters such as strength, ductility, fracture resistance, wear resistance and fatigue resistance;

(g) **surface properties**; and

(h) the confirmation that the device meets any **defined chemical and/or physical specifications**.

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.2

The devices must be designed, manufactured and packed in such a way as to **minimize the risk posed by contaminants and residues** to the persons involved in the transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. **Particular attention must be paid to the tissues exposed and the duration and frequency of the exposure**.

MDR GSPR 10.2

Devices shall be designed, manufactured and packaged in such a way as to **minimise the risk posed by contaminants and residues** to patients, taking account of the intended purpose of the device, and to the persons involved in the transport, storage and use of the devices. **Particular attention shall be paid to tissues exposed** to those contaminants and residues **and to the duration and frequency of exposure**.

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.5

The devices must be designed and manufactured in such a way as to **reduce to a minimum the risks posed by substances leaking from the device**.

ISO 10993-1: evaluation of wear particles, degradation products and process residues is required

MDR GSPR 10.4.1

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.**

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.5

If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain **phthalates which are classified as** [**CMR**]…these devices **must be labelled** as a device containing phthalates…

MDR GSPR 10.4.1

Devices / parts / materials that:
– are invasive and come into direct contact with the human body,
– (re)administer medicines, body liquids or other substances, or
– transport or store medicines, body fluids or substances:

shall only contain [**CMR substances**] **in a concentration above 0.1%** …

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.5

Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction

No requirements for justification or labelling of toxic substances other than phthalates

MDR GSPR 10.4.1

Devices / parts / materials that:
- are invasive and come into direct contact with the human body,
- (re)administer medicines, body liquids or other substances, or
- transport or store medicines, body fluids or substances:

shall only contain [**CMR substances**] **in a concentration above 0.1%** …

(labelling and justification requirements apply)

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.5

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

MDR GSPR 10.4.5

Where devices, parts thereof or materials used therein [that are invasive or administer substances] contain [**CMR substances** above 0.1%] the presence of those substances **shall be labelled**… with the list of such substances

(repeat of 10.4.1)

Comparison: GSPRs vs ERs or ISO 10993

MDD ER 7.5

If intended use of devices containing [**phthalates**] includes [**vulnerable populations**]:

- a **specific justification** for the use of [**phthalates**] with regard to compliance with the ERs
- **information on residual risks** for vulnerable populations and appropriate **precautionary measures** in the IFU

MDR GSPR 10.4.5

If intended use of devices containing **CMR 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

Comparison: GSPRs vs ERs or ISO 14971

ISO 14971

Risk-based justification is consistent with the risk management principles set out in ISO 14971:2020, e.g. benefit-risk assessment

Exposure estimate – ISO 10993-18

Analysis of alternatives – ISO 10993-17

Acceptability criteria – ISO 14971

Committee guidelines – ISO 14971

MDR GSPR 10.4.2

Justification shall be based upon:

(a) an estimate of exposure;

(b) an analysis of alternatives (including available research)

(c) justification in relation to functionality, performance and benefit-risk ratio (including use in vulnerable populations)

(d) scientific committee guidelines

Comparison: GSPRs vs ERs or ISO 10993

MDD

N/A

MDR GSPR 10.4.3 & 10.4.4

Guidance on phthalates, CMR substances and endocrine disruptors to be developed by the relevant scientific committee

Rationale for CMR provisions

- The potential harm is severe, with the possibility of irreversible effects
  - Applies to substances that are **carcinogenic, mutagenic or toxic to reproduction** (including **endocrine disruptors**)
    - category 1A or 1B (Part 3, Annex VI, Classification, Labelling and Packaging Regulation (1272/2008))
    - endocrine disruptors for which there is scientific evidence of probable serious effects to human health (e.g. endocrine disruptors that are toxic to reproduction, such as DEHP)
- Some CMR substances do not have a widely accepted safety threshold
- Concern is for susceptible or vulnerable populations
- The objective is transparency

But: Requirements for labelling and justification of certain toxic substances, irrespective of exposure, are not in line with risk management principles

Regulation based on hazard instead of risk is a political decision

Implications of CMR provisions

- A risk-based justification remains acceptable
  - The risk estimate is based on the level of exposure to the hazard
  - A hazardous situation occurs when someone is exposed to a hazard
  - If exposure from the device is below a recognised threshold there is no hazardous situation
  - If there is no hazardous situation, there is no risk
  - However, if no threshold can be identified, exposure should be reduced as much as possible, while maintaining the benefit-risk balance
- The risk needs to be outweighed by a specific benefit arising from the use of a CMR substance, that cannot feasibly be met by other design solutions, e.g.
  - Extreme flexibility needed for specific procedures; extension of the lifespan of erythrocytes
  - Physical damage to device materials by alternative methods of sterilization
    - Note that this means that EtO should not be used if alternatives are acceptable

The implications of a risk management process

- "This risk management process involves identification of biological hazards, estimation of the associated biological risks, and determination of their acceptability"
  (ISO 10993-1:2018 Clause 4.1)
- ISO 14971 is a normative reference of ISO 10993-1 and therefore specifies the required risk management process
- A biological evaluation must therefore only be conducted in line with a clearly specified risk management process
  - A box-checking process based on biological testing is no longer acceptable (it never was!)
  - The process starts with hazard identification (i.e. the presence of constituents of toxicological concern)
  - If there are no toxicological hazards, there can be no toxicological risks!

MedPass International S.A.S

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Thank you

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