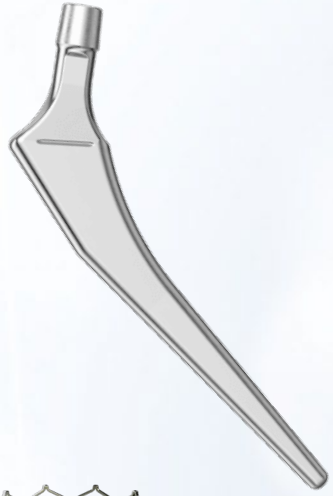
Welcome to

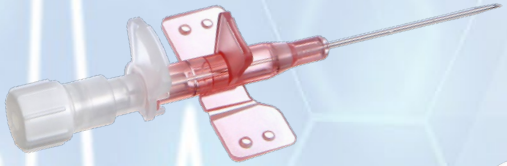
# EMERGING TECHNOLOGIES CONFERENCE at Advanced Textiles EXPO®

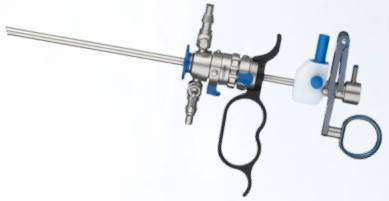
# Medical Product vs. Device
## A look behind the scenes

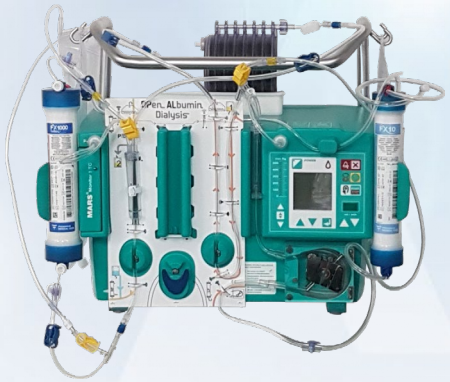
HOHENSTEIN
MEDICAL

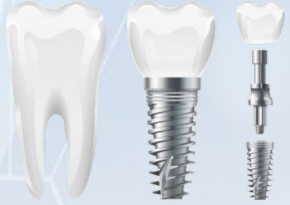
# The Complex World of Medical Devices



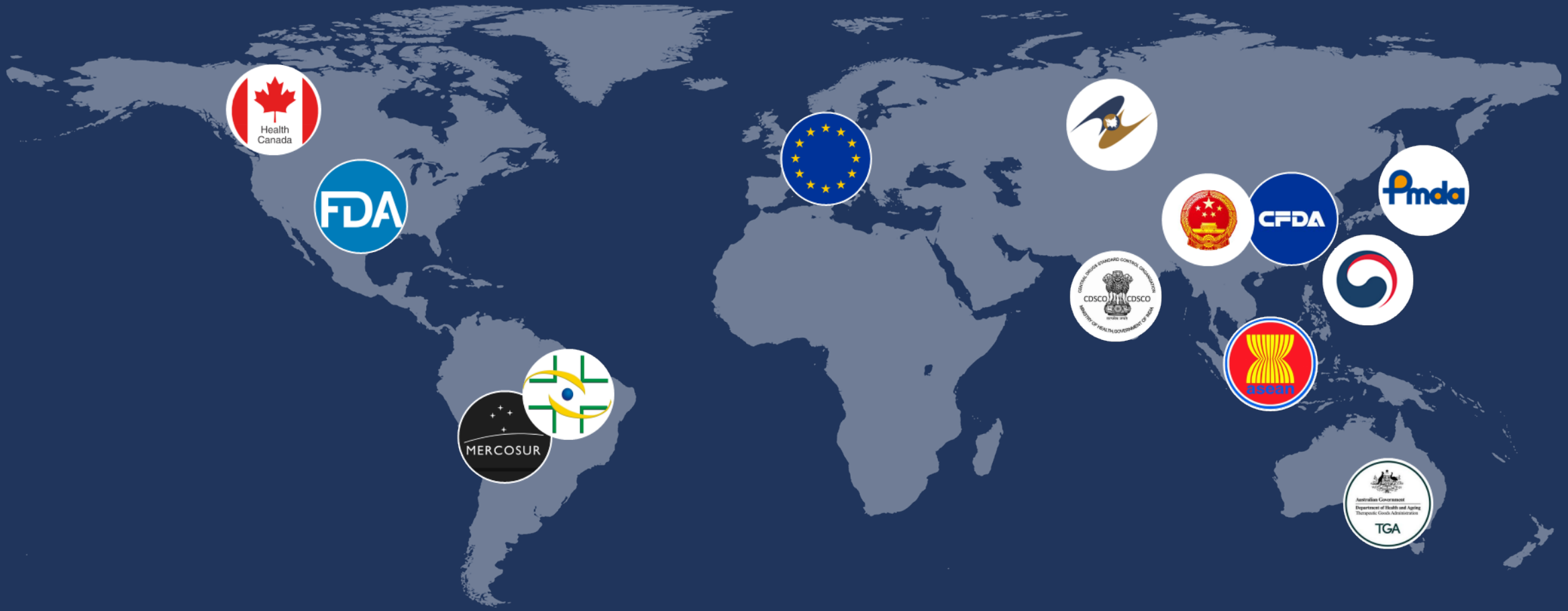






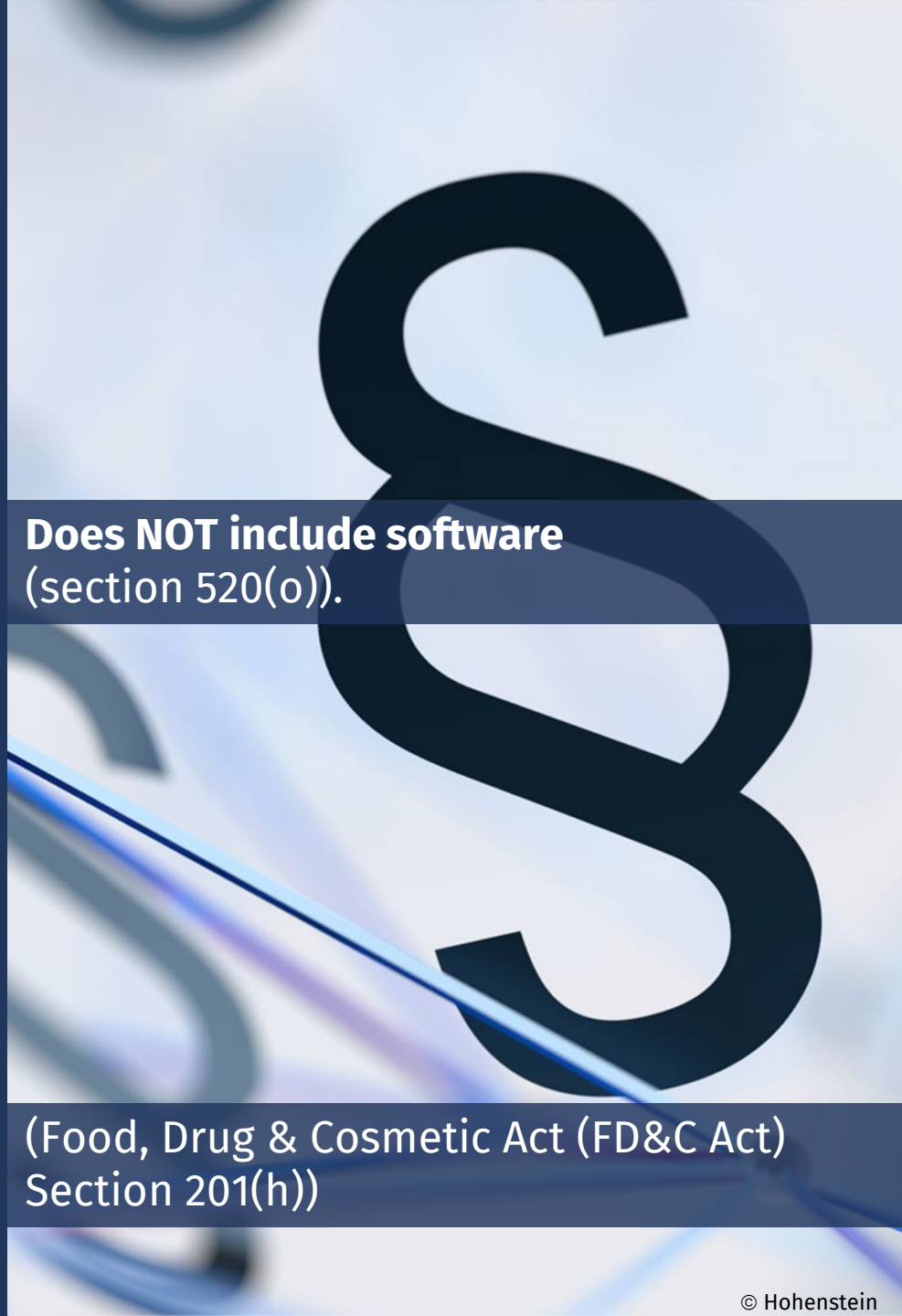
# Global Regulations
## Medical Devices



# FDA Definition "Device”
## U.S. Food and Drug Administration

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- **intended for use** in the diagnosis of disease or other conditions, or in the **cure, mitigation, treatment, or prevention** of disease in man or other animals, or
- intended to **affect the structure or any function of the body** of man or other animals
- does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes



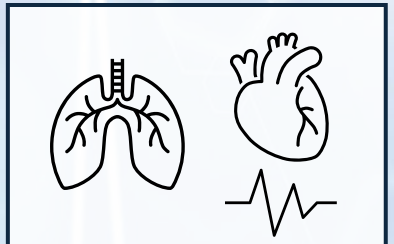
**Does NOT include software** (section 520(o)).

(Food, Drug & Cosmetic Act (FD&C Act) Section 201(h))

# Medical Device Classification

U.S.

**Class 3**
High risk

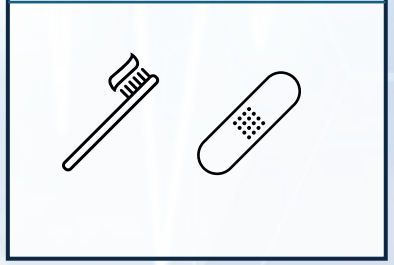


Implants
Stents
Pacemaker

**Class 2**
Moderate risk

Medical gloves
Defibrilator
Blood pressure monitor

**Class 1**
Low risk



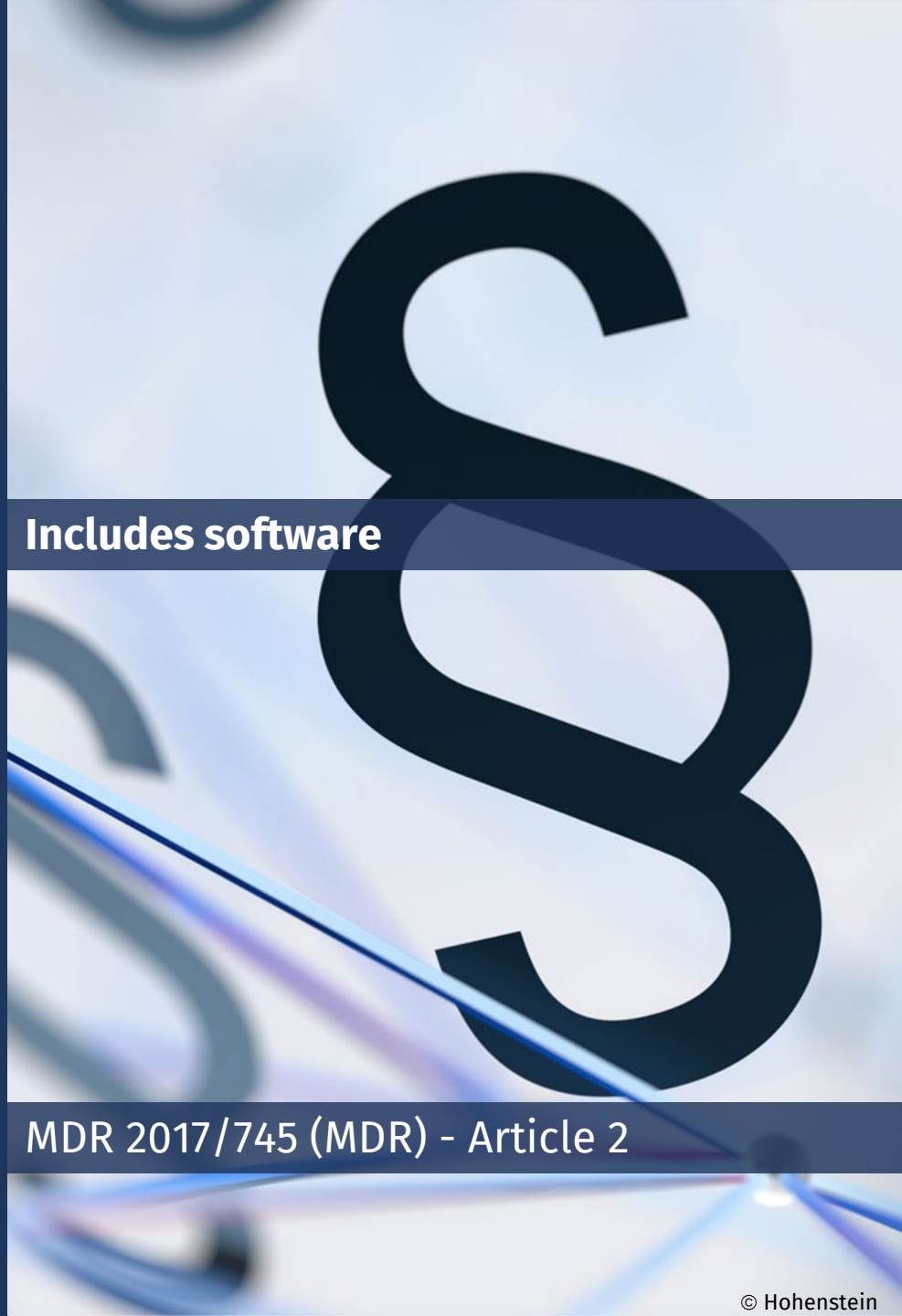
Toothbrush
Hygiene products
Patches

# EU Definition "Medical Device”
## Medical Device Regulation (MDR)

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- **diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease**,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an **injury or disability**,
- **investigation, replacement or modification of the anatomy or of a physiological or pathological process** or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which **does not achieve its principal intended action by pharmacological, immunological or metabolic means**, in or on the human body, but which may be assisted in its function by such means.

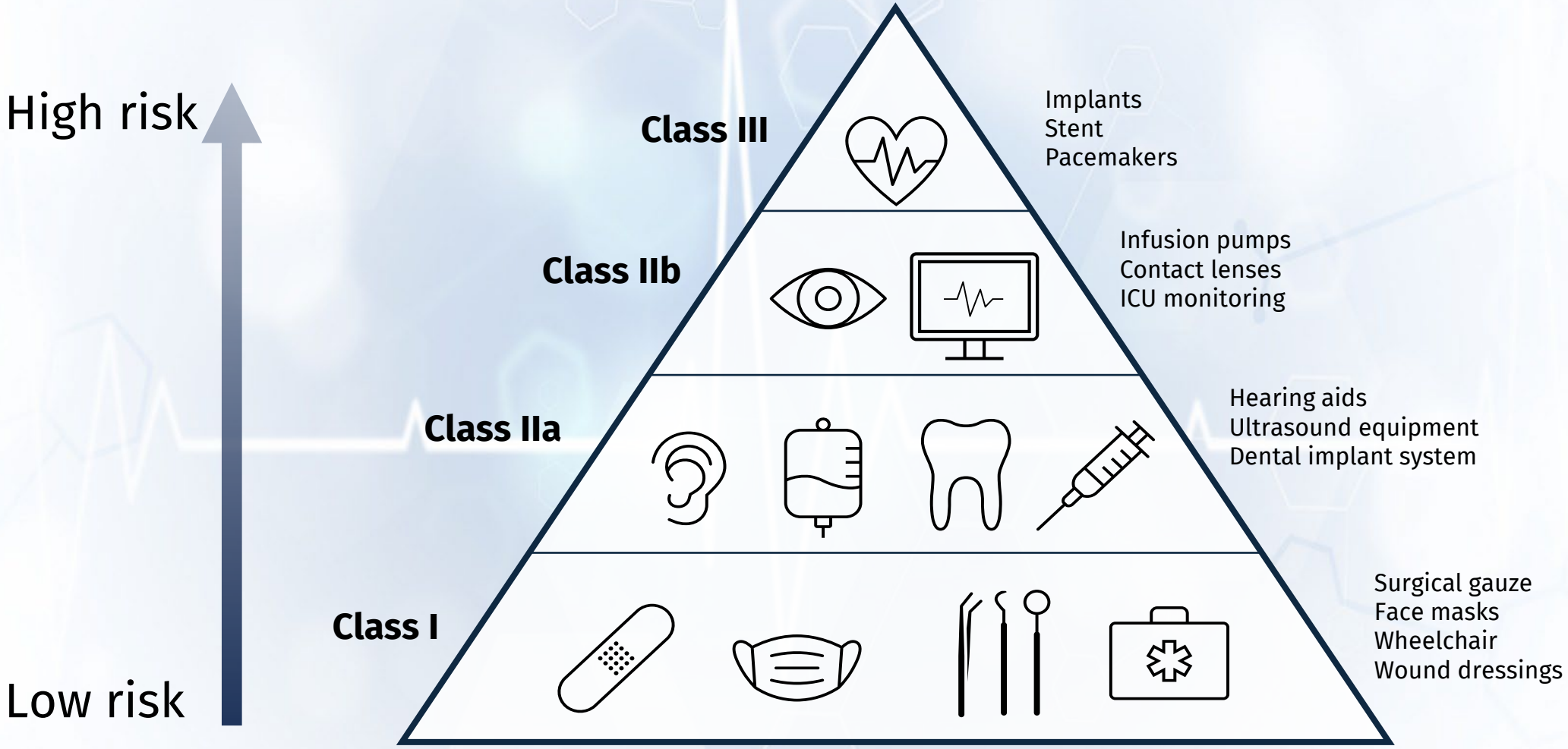


**Includes software**

MDR 2017/745 (MDR) - Article 2

# Medical Device Classification

EU



# Medical Device – Yes or No?


- "Self-massage and training of tissues”
- "Enhances blood circulation and releases muscle tensions”

**→ Medical Device**


- "Self-massage”
- "Improved well-being”

**→ NOT Medical Device**

# Medical Device – US vs EU

## US

**Unscented Tampon**
Reproductive, Gynecology and Urology Devices (DHT3B)

→ **Medical Device Class 2**
Guidance Document (FDA-2020-D-0957)

## EU

**Menstrual Products**
Hygiene Products

→ **NOT Medical Device**

# **Approval**
## FDA vs EU MDR

### Different

- Classification system
- Submission process
- Labeling placed on medical devices
- Documentation & evaluation required

### Both

Require quality management system

# It’s a Medical Device!
## Now What?

Prove it’s safe.

# Biocompatibility

## ISO 10993 Definition:

The ability of a device material to **perform** with an **appropriate host response** in a specific situation.

→ Direct and/or indirect **contact with the body**

→ Is my material biocompatible?

## EU MDR Obligation

ANNEX II, CHAPTER 6.1

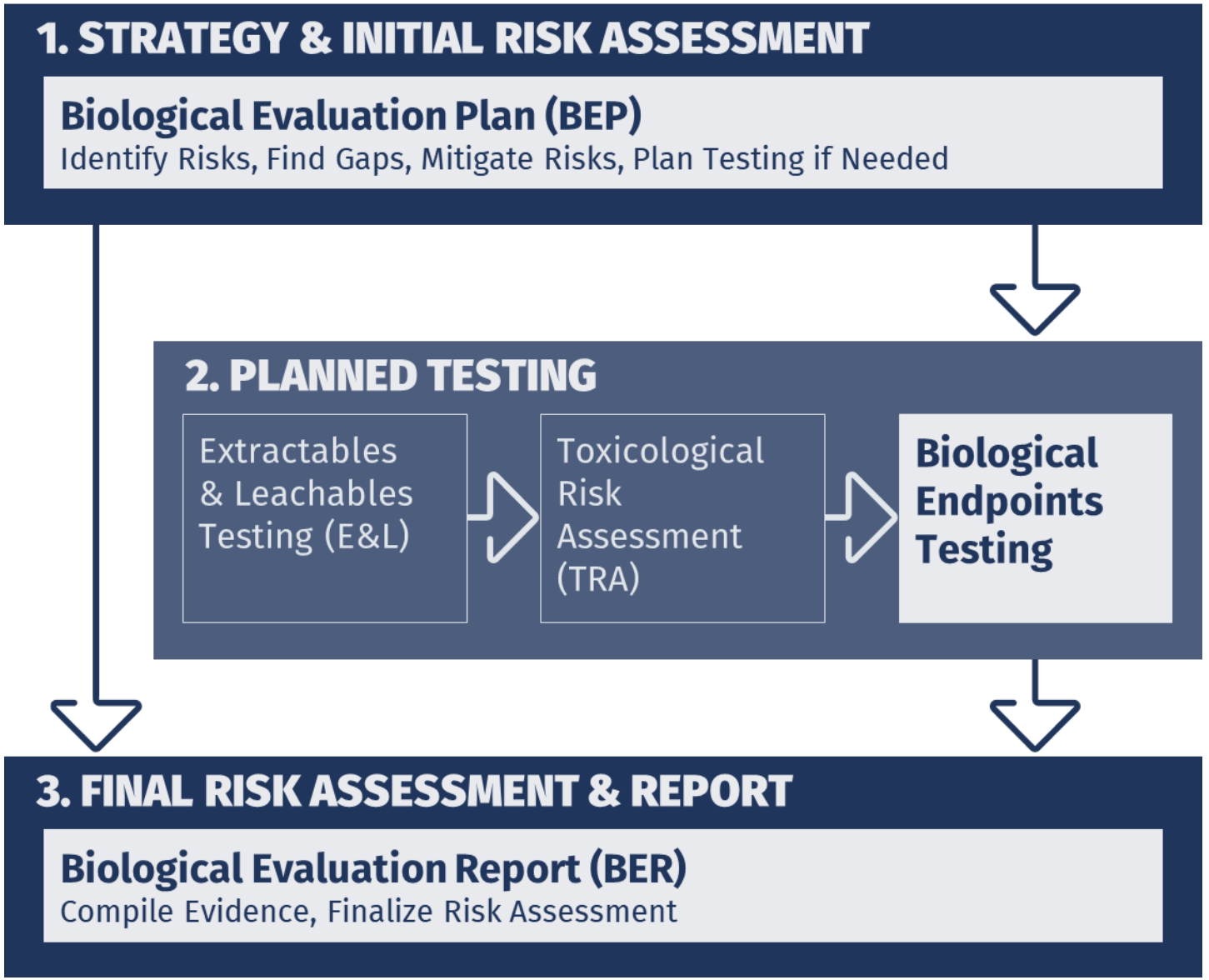
manufacturers to evaluate the biocompatibility of their device materials and to document the results
MDR, Annex II, Chapter 6.1.

→ ISO 10993: Biological evaluation of medical devices

→ ISO 18562: Biocompatibility of gas pathway contacting devices

# **Ensuring Biological Safety**
of Medical Devices

# Medical Device Biocompatibility Process



# Targeting vs. Screening
## Why do both exist?

### Targeting
The Specific Search

- Search for specific substance
- Often specific limits (w/w)
- Use of external reference substance
- Qualitative & quantitative results

**Is substance X present in concentration C?**

### Screening
The General Search

- Search for "all" substances
- Individual limits (AET)
- Use of surrogate standards
- Semi-qualitative & -quantitative results
  - Challenge: "Unknowns"

**Are substances above limit A present?**

# Chemical Analysis

## Target Analysis with RSL

**Restricted Substance List (RSL)**
Substance-specific limits

**Selected Medium**

Suitable extraction medium

**Extraction**

ICP-MS,
GC-MS,
HPLC-MS

**Analytical Testing**
Suitable analysis device with reference standard

# Chemical Screening
ISO 10993-18

**Analytical Evaluation Threshold**
Product-specific AET Calculation

**Selected Medium**

polar,
semi-polar,
non-polar

**Extraction**
24-72 h

**Analytical Testing + Database Matching**

ICP-MS,
GC-qTOF,
HPLC-qTOF

**List Substances Above AET**
Not Pass/Fail

# Chemical Screening

## Diverse Techniques for Diverse Questions

### ISO 10993-12/18

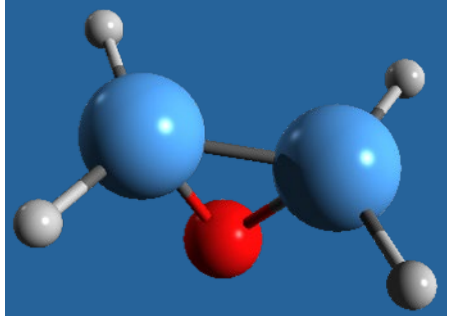
**Gas chromatography**
TDS-MS; HS-MS; GS-MS/MS; GC-QTOF

**Liquid chromatography**
LC-QTOF; LC-MS; LC-MS/MS

**Inductively coupled plasma**
ICP-MS

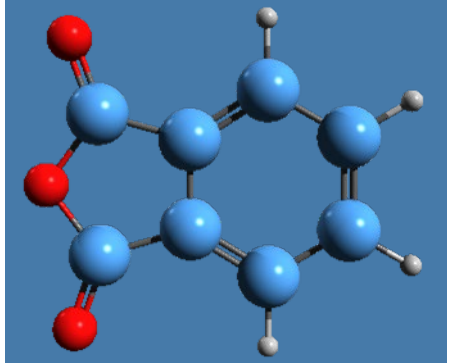
### (V)VOC Screening

(Very) Volatile Organic Substances



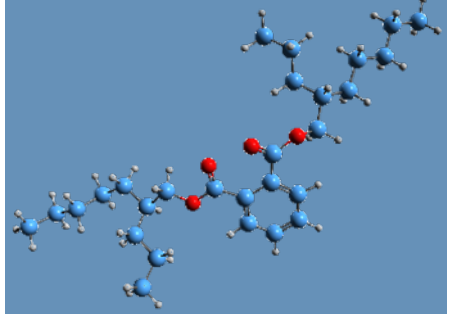
### SVOC Screening

Semi-volatile Organic Substances



### NVOC Screening

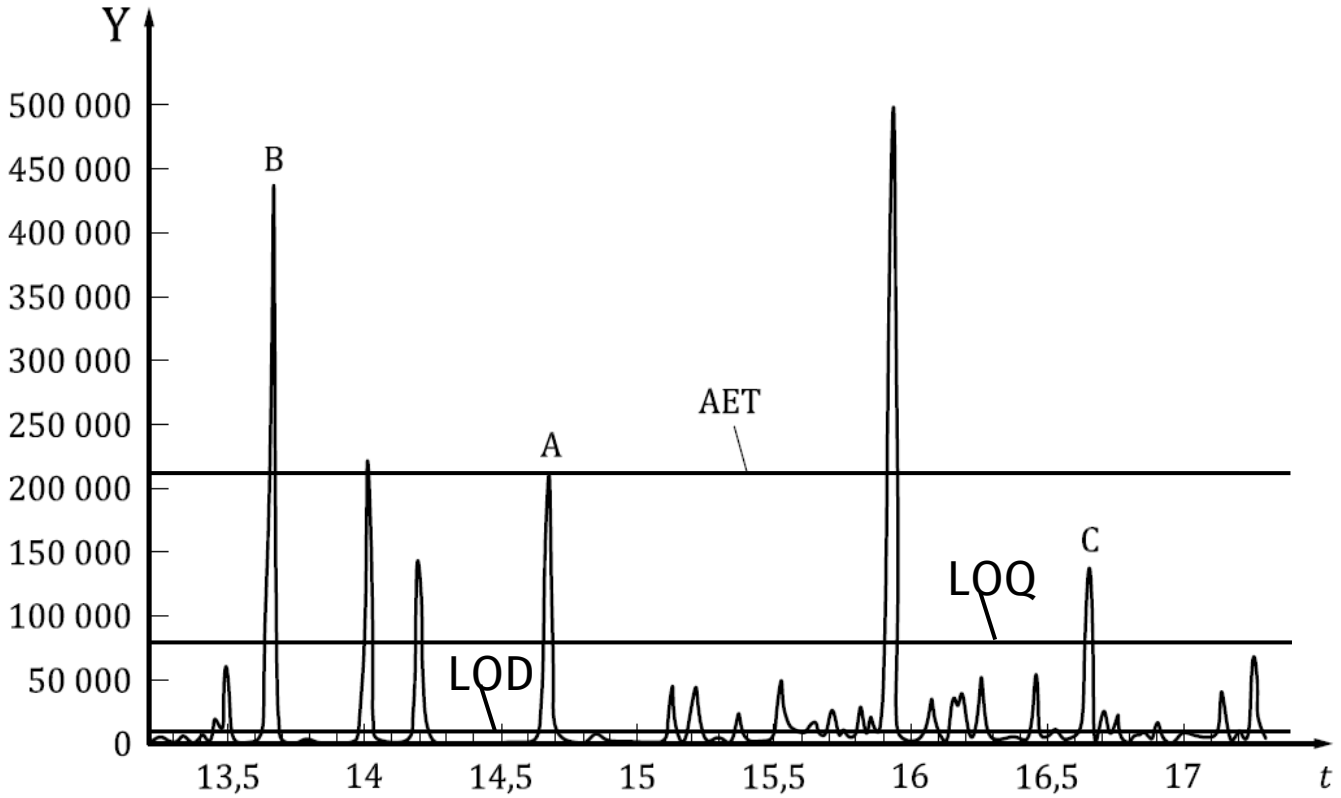
Non-volatile Organic Substances



### ICP

Elements & Metals

# From Chemistry to Toxicology
- A Translation Tool




## AET

**Analytical Evaluation Threshold**

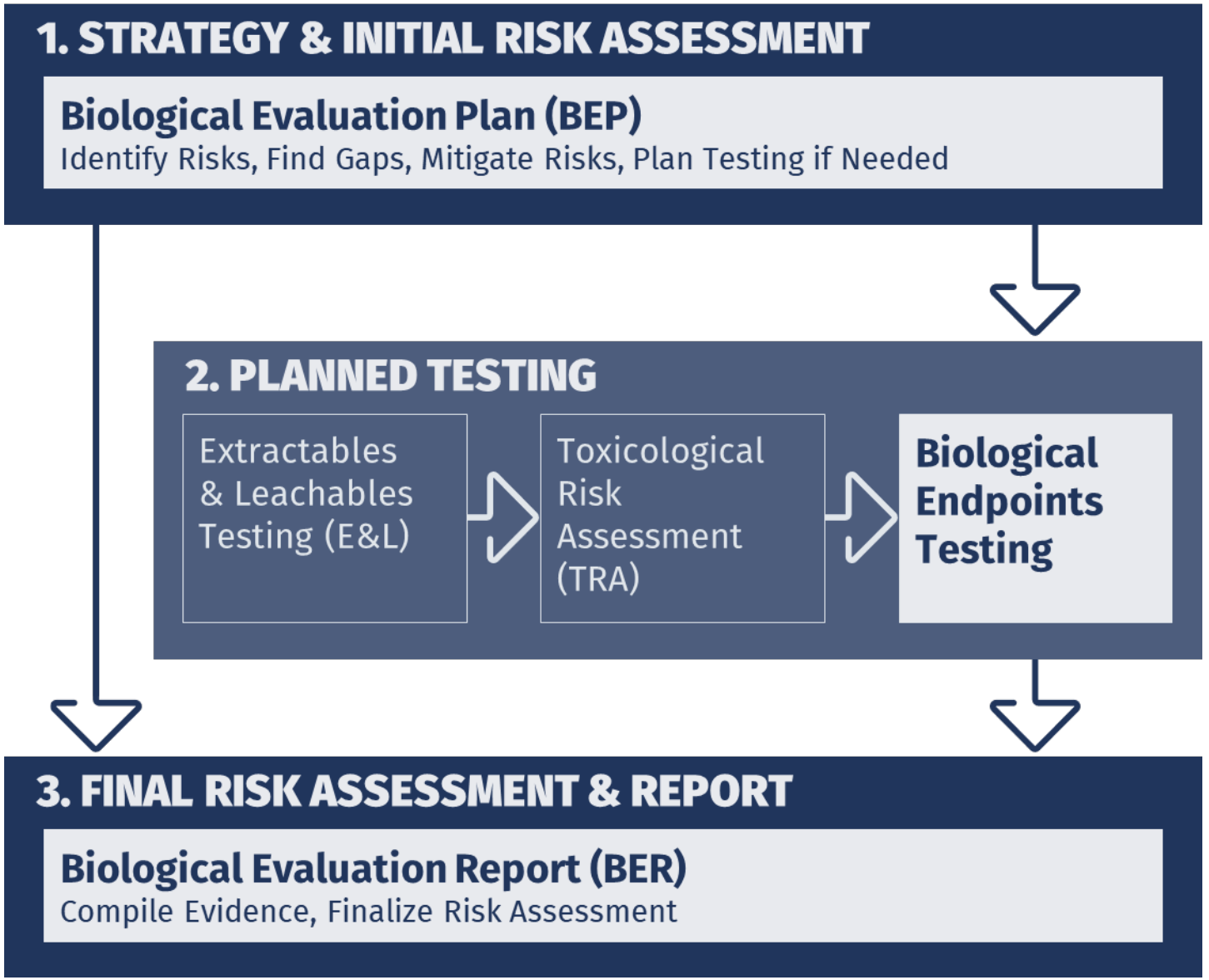
Value above which detected substances **must be evaluated** toxicologically

$$\mathrm{AET} = \frac{\mathrm{DBT} \cdot \frac{\mathrm{A}}{\mathrm{BC}}}{\mathrm{UF}}$$

# **Toxicological Risk Assessment**
## Are there any hazards?

- **List** all detected substances above AET
- Gather **toxicological data** from literature/database
- Determine **max tolerable exposure** (tolerable intake, TI)
  → If unknown, use threshold of toxicological concern (**TTC**)
- Estimate patient **exposure** (daily amount released)
- Calculate **margin of safety** (MoS): TI / Exposure
  → MoS > 1 (“acceptable”)
  → MoS < 1 (further data/risk management required)

# **Risk Control**
Gap Analysis



# Risk Analysis
## Determination of relevant endpoints for evaluation

**Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"**

**Guidance for Industry and Food and Drug Administration Staff**

**Document issued on: September 8, 2023.**

**Table A.1: Biocompatibility Evaluation Endpoints**

| Medical device categorization by | | | Biological effect | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nature of Body Contact | | Contact Duration | | | | | | | | | | | | | |
| Category | Contact | A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – long term (> 30 d) | Cytotoxicity | Sensitization | Irritation or Intracutaneous Reactivity | Acute Systemic Toxicity | Material-Mediated Pyrogenicity | Subacute/Subchronic Toxicity | Genotoxicity | Implantation | Hemocompatibility | Chronic Toxicity | Carcinogenicity | Reproductive/Developmental Toxicity# | Degradation@ |
| Surface device | Intact skin | A | X | X | X | | | | | | | | | | |
| | | B | X | X | X | | | | | | | | | | |
| | | C | X | X | X | | | | | | | | | | |
| | Mucosal membrane | A | X | X | X | | | | | | | | | | |
| | | B | X | X | X | X | O | X | | X | | | | | |
| | | C | X | X | X | X | O | X | X | X | | X | | | |
| | Breached or compromised surface | A | X | X | X | X | X | | | | | | | | |
| | | B | X | X | X | X | X | X | | X | | | | | |
| | | C | X | X | X | X | X | X | X | X | | X | X | | |

# Risk Management – Biological Endpoints

## Implementing Smart Biocompatibility Lab Strategies

**Systemic Toxicity**
(10993-11)

**CMR**
Carcinogenic, Mutagenic, & Reprotoxic Substances
(10993-3)

**Local Toxicity**
(10993-23, -10)

**Immunotoxicity**
(10993-20)

**Hemocompatibility**
(10993-4)

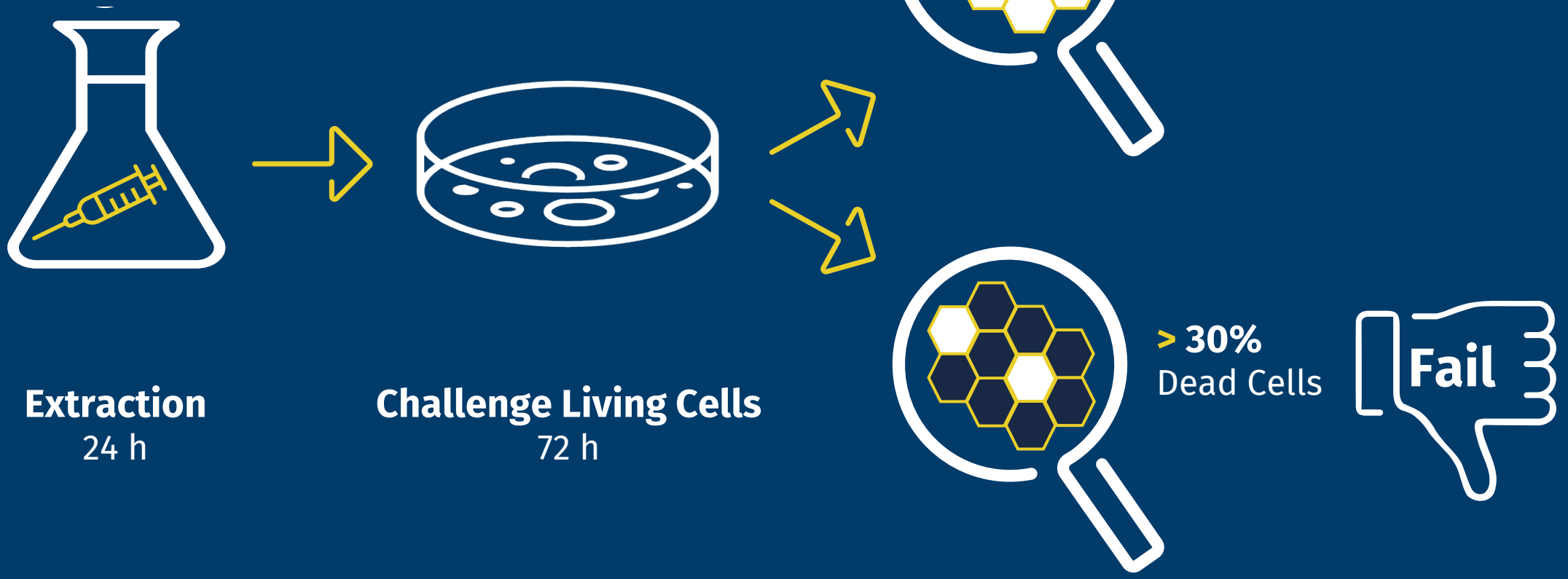
**Cytotoxicity**
(10993-5)

**Physical properties**
e.g., particles (10993-22)

**Implantation Effects**
(10993-6)

**Morphology**
(10993-19)

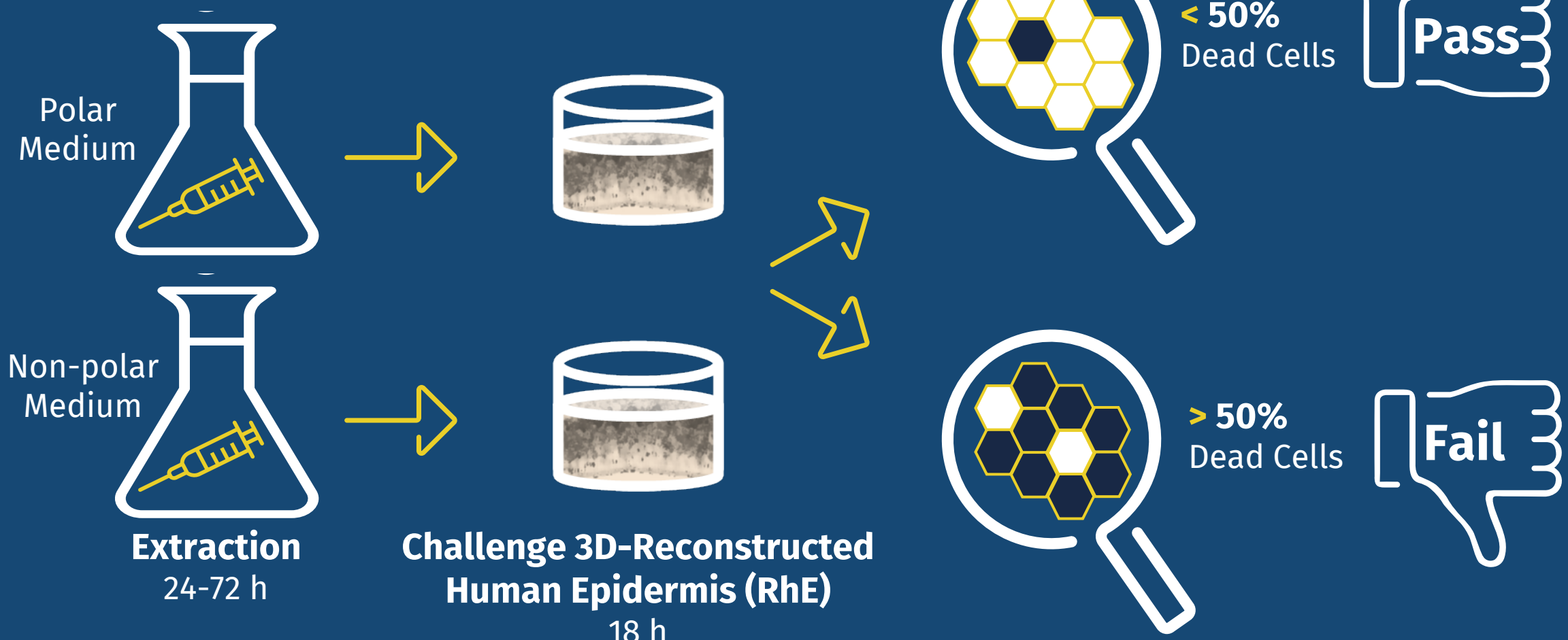
# Cytotoxicity
ISO 10993-5




**Extraction**
24 h

**Challenge Living Cells**
72 h

# Skin Irritation
## ISO 10993-23



# Skin sensitization (in vitro)

## ISO 10993-10 Annex C

**Extraction**
24-72 h
In cell culture medium

**Treatment of cells with extract**

No activated immune markers


activated immune markers

# Questions?

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SCAN FOR
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*See you next year!*

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