Webinar Thursday, May 16, 2024

Hosted by the SOT Medical Device and Combination Product Specialty Section

Biological Evaluations for European Union Medical Device Regulation

Challenges, Experiences and Tips

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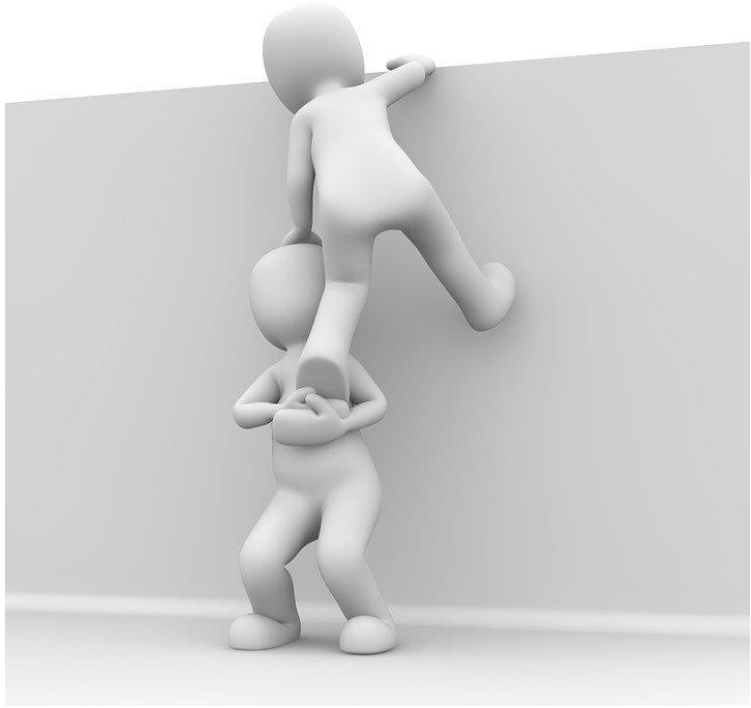
Biological Evaluation for EU MDR

Outline

- Backgrund to EU MDR 2017/745
- Differences EU MDR / MDD / US FDA
- Main GSPR*s related to biological safety
- Where to find information
- Challenges, Experiences and Tips – Summary



**GSPR – General Safety and Performance Requirements*

Disclaimer

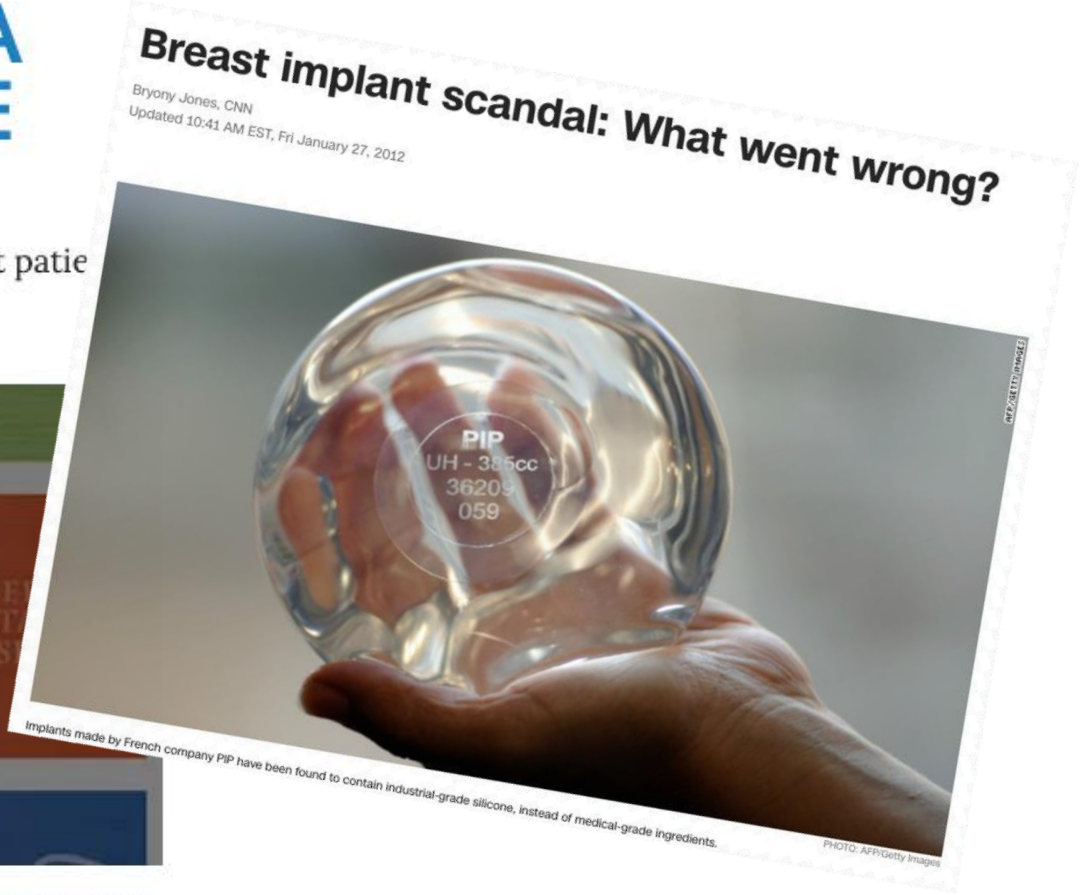
This presentation include views of the presenters that are not necessarily those of Veranex.

Backgrund to EU MDR 2017/745

From a scandal to MDR

PIP BREAST IMPLANT SCANDAL: A STORY THAT TRIGGERED CHANGE

The Poly Implant Prothese (PIP) Breast Implant Scandal is one of the most significant patie
protection failures in the history of clinical research.



As traumatic as it was for the patients involved, it has also been credited in part for triggering significant regulatory changes in the European Union—including the new EU MDR requirements.

Adopted from
CNN https://edition.cnn.com/2012/01/27/world/europe/pip-breast-implant-scandal-explained/index.html
+Mass Device https://www.massdevice.com/pip-breast-implant-scandal-story-triggered-change/

Quality
Transparency
Follow-up

Breast implant scandal: What went wrong?

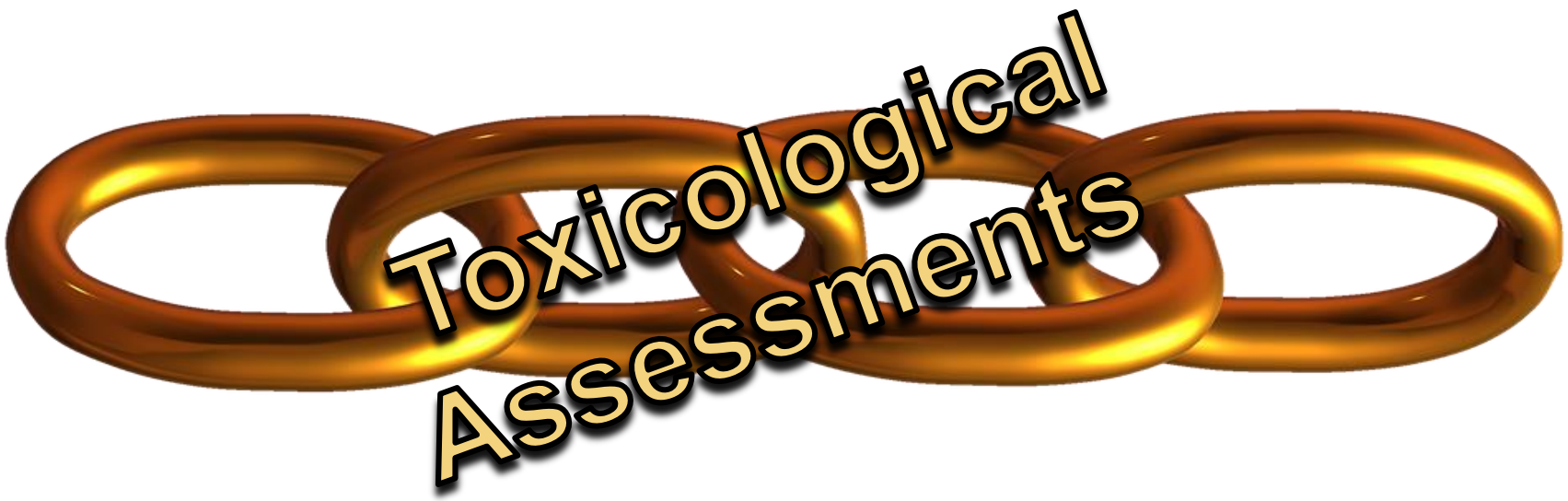
Bryony Jones, CNN
Updated 10:41 AM EST, Fri January 27, 2012

PHOTO: AFP/Getty Images

Implants made by French company PIP have been found to contain industrial-grade silicone, instead of medical-grade ingredients.

MDR

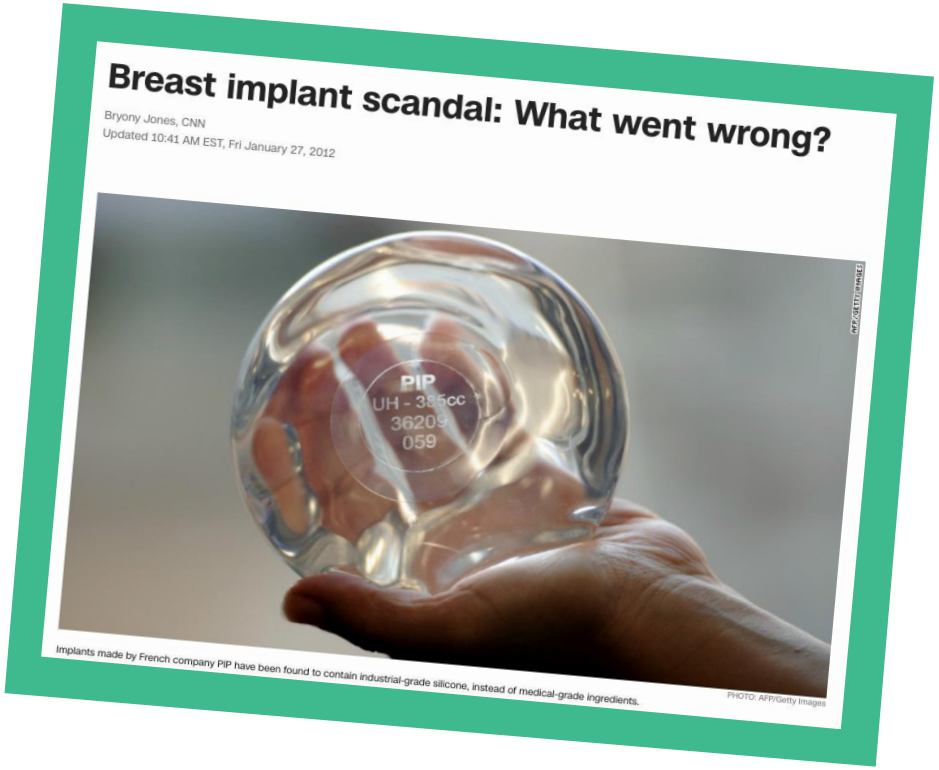
Quality control Chemical data Biological safety



Differences EU MDR / MDD / US FDA

MDR vs MDD – overall

- Quality control
- Documentation and justifications
- Clinical data
- Post Market Surveillance
- No grandfathering – reassessment of TD (Technical Documentation)



~~**ER (Essential Requirements)**~~

GSPR (General Safety and Performance Requirements)

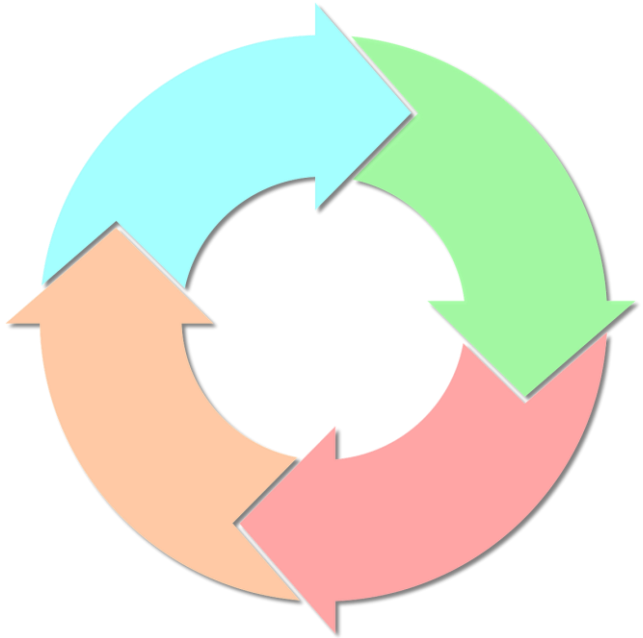
MDR vs MDD

- Reclassification of many medical devices to a
  - **higher risk class** (substance based devices) and
  - a **new classification** for reusable surgical devices requiring notified body oversight

- The scope is broadened to include
  - **non-medical and cosmetic devices** not previously regulated. Examples include products for cleaning, disinfection or sterilization of devices as well as cosmetic contact lenses, liposuction equipment, or epilation lasers.

New or increased emphasis

- Choice of material in design
- Total lifecycle including during use
- Particles, especially nano-size
- For whom risks need to be assessed
- CMR/ED and labeling
- GSPR 12.2 (as per Rule 21) – ADME



MDR vs MDD – overall / Rule 21

Devices composed of substances intended to be introduced into the human body via a body orifice or appli**ed to the skin and that are absorbed by or locally dispersed** in the human body are classified as:

- class III substance or metabolite systemically absorbed to achieve the intended purpose
- class III achieve intended purpose in the stomach or lower gastrointestinal tract and substance or metabolite systemically absorbed
- **class IIa** applied to the skin or in the nasal or oral cavity as far as the pharynx, and achieve intended purpose on those cavities
- class IIb in all other cases

Note, there are exceptions!

EU MDR

- No devices will be eligible for grandfathering under the MDR
- MDR requirements will hold your documentation to the latest standards, but your testing procedure may not be held to those standards
- Identifying carcinogens, mutagens, reproductive toxicants and endocrine disruptions applies at 0.1% w/w or above to all invasive devices, regardless of contact duration or class
- Clearly address ADME for substance based devices (Rule 21)

US FDA vs MDR

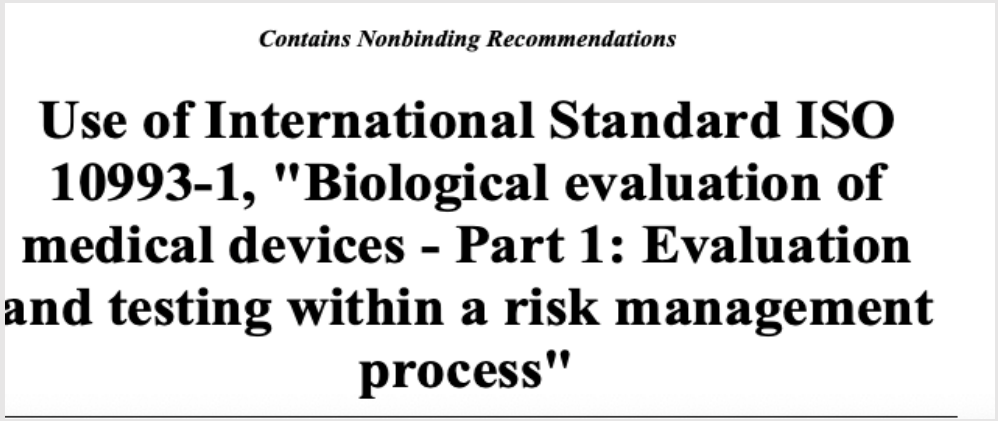
- Testing on device in Final Finished Form
  - Thorough justifications for all deviations (not always sufficient)
- Consider worst case exposure (beyond theoretically possible)
- Additional requirements on chemical analyses
  - Such as, UF factors and number of surrogate standards
- EU MDR has clearer requirements when it comes to such as evaluation of total life cycle, substance based devices, and specific once for CMR/ED substances

Recognized Consensus standards – FDA

This standard is relevant to medical devices and is recognized on its scientific and technical merit and/or because it supports existing regulatory policies.

This standard is recognized in part because:
Table A.1 in Annex A is in conflict with an existing published final guidance, see Attachment A, Table A1 of the guidance listed below.

https://www.fda.gov/media/85865/download


Contains Nonbinding Recommendations

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

EU MDR – Biocompatibility

- Harmonized standard – presumption of conformity with respective GSPRs (MDR article 8)

Article 8

Use of harmonised standards

1. Devices that are in conformity with the relevant harmonised standards, or the relevant parts of those standards, the references of which have been published in the *Official Journal of the European Union*, shall be presumed to be in conformity with the requirements of this Regulation covered by those standards or parts thereof.

MDR (Annex I, Ch1) – Methods shall take in to account the **”generally acknowledged state of the art“**

EU MDR – Biocompatibility

https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards_en

Legislation reference (A)	ESO (B)	Reference number of the standard (C)	Title of the standard (D)	Date of start of presumption of conformity (1)	OJ reference for publication in OJ (2)	Restriction (3)	Date of start of presumption of conformity with restriction (4)	OJ reference for publication of a restriction in OJ (5)	Date of withdrawal from OJ (end of presumption of conformity) (6)	OJ reference for withdrawal from OJ (7)
2017/745	CEN	EN ISO 10993-9:2021	Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products (ISO 10993-9:2019)	05/01/2022	OJ L 1 - 05/01/2022	-		-		-
2017/745	CEN	EN ISO 10993-10:2023	Biological evaluation of medical devices - Part 10: Tests for skin sensitization (ISO 10993-10:2021)	05/07/2023	OJ L 170 - 05/07/2023	-		-		-
2017/745	CEN	EN ISO 10993-12:2021	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials (ISO 10993-12:2021)	05/01/2022	OJ L 1 - 05/01/2022	-		-		-
2017/745	CEN	EN ISO 10993-15:2023	Biological evaluation of medical devices - Part 15: Identification and quantification of degradation products from metals and alloys (ISO 10993-15:2019)	08/03/2024	OJ L, 2024/815 - 08/03/2024	-		-		-
2017/745	CEN	EN ISO 10993-17:2023	Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents (ISO 10993-17:2023)	08/03/2024	OJ L, 2024/815 - 08/03/2024	-		-		-
2017/745	CEN	EN ISO 10993-18:2020, EN ISO 10993-18:2020/A1:2023	Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process (ISO 10993-18:2020)	08/03/2024	OJ L, 2024/815 - 08/03/2024	-		-		-
2017/745	CEN	EN ISO 10993-23:2021	Biological evaluation of medical devices - Part 23: Tests for irritation (ISO 10993-23:2021)	19/07/2021	OJ L 256 - 19/07/2021	-		-		-

Annex VII REQUIREMENTS FOR NOTIFIED BODIES

The Notified Body shall have documented procedures in place for the review…

- the planning, conduct, assessment, reporting and, where appropriate, updating of the pre-clinical evaluation, in particular of
- the scientific pre-clinical literature search, and
- the pre-clinical testing, for example laboratory testing, simulated use testing, computer modelling, the use of animal models,
- the **nature and duration of body contact and the specific associated biological risks**
- the **interface with the risk management process**, and
- the appraisal and analysis of the available pre-clinical data and its relevance with regard to **demonstrating conformity with the relevant requirements in Annex I (GSPR)**

Main GSPRs related to biological safety

MDR – Biocompatibility ANNEX I

GSPR 10 Chemical, physical and biological properties

- Selection of materials/substances regarding toxicity
- Compatibility with body

GSPR 10.2

- Minimise the risk posed by contaminants and residues (manufacturing, packaging, storage)

GSPR 10.4.1

- Reduce as far as possible the risk posed by released substances or particles; 0.1% w/w threshold CMRs and EDs

GSPR 10.6

- Reduce as far as possible the risks linked to size and properties of particles, special attention to nanomaterial

MDR – Biocompatibility ANNEX I

GSPR 1	Safety of patients and users
GSPR 4	Safe design and manufacture, risk-based approach
GSPR 6	Lifetime of the device
GSPR 7	Transport and storage (eg temperature and humidity)
GSPR 12	Medicinal substances and substances introduced to the human body (ADME)
GSPR 13	Materials of biological origin
GSPR 14.2	Risks from (eg) Accidental ingress of substances, Aging

Quality control – Choice of material in design

GSPR	Specifics	Comment
# 4	"… In selecting the most appropriate solutions, manufacturers shall, in the following order of priority: (a) **eliminate or reduce risks as far as possible through safe design and manufacture**"	**Chemical information – material assessments** NB to assure device manufacturer is using the latest scientific knowledge, including about the biocompatibility of materials (See Annex VII)

Total life cycle

GSPR	Specifics	Comment
# 6.7	”…during the **lifetime of the device**, …” ”… during **transport and storage**, for example, through **fluctuations of temperature and humidity**, taking account of the instructions and information provided….”	Consider fluctuations in conditions **Chem info – compatibility** **Analyses may be needed**
# 10.3	“…used safely with the **materials and substances, including gases**, with which they enter into contact during their intended use; if intended to administer medicinal products …**compatible with the medicinal products** concerned…”	
# 10.6	” …reduce as far as possible the risks linked to the **size and the properties of particles** which **are or can be released** into the patient's or user's body, unless … intact skin only. Special attention … to **nanomaterials**.”	Both present from beginning and due to wear and degradation

For whom risks need to be assessed

GSPR	Specifics	Comment
# 1	”… shall not compromise the clinical condition or the **safety of patients**, or the safety and health of **users** or, where applicable, **other persons**,….”	Broader than ISO 10993-1 Addressed in risk analysis with assessment when deemed needed E/L and TRA? Consider multiple sourcing (suppliers, contractors)
# 10.2	“Devices shall be **designed, manufactured and packaged** in such a way as to **minimize 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…”	

GSPR #10.4.1 CMR-ED substances

Devices or parts thereof or those materials used therein that are:
invasive or (re)administer, stor or transport medicines, body liquids or other substances, including gases

If **> 0.1 % (w/w)** of:

- **CMR Class 1A or 1B**
  (carcinogenic, mutagenic or toxic to reproduction)

- **ED** (endocrine-disruptors)

Requires assessment, justification, and labelling

GSPR #10.4.1 ≠ SVHC

Total composition!

If Yes > 0.1 % w/w – Provide Justification for Use / Label

Patient Safety Assessment

- Estimation of potential patient or user exposure

  Worst case or E/L study

Is 0.1 w/w % a concern?

1000 ug/g or 1 mg/g

Material Replacement/Redesign possible?

- Analysis of possible alternative substances,

  Including information about independent research, peer-reviewed studies, scientific opinions

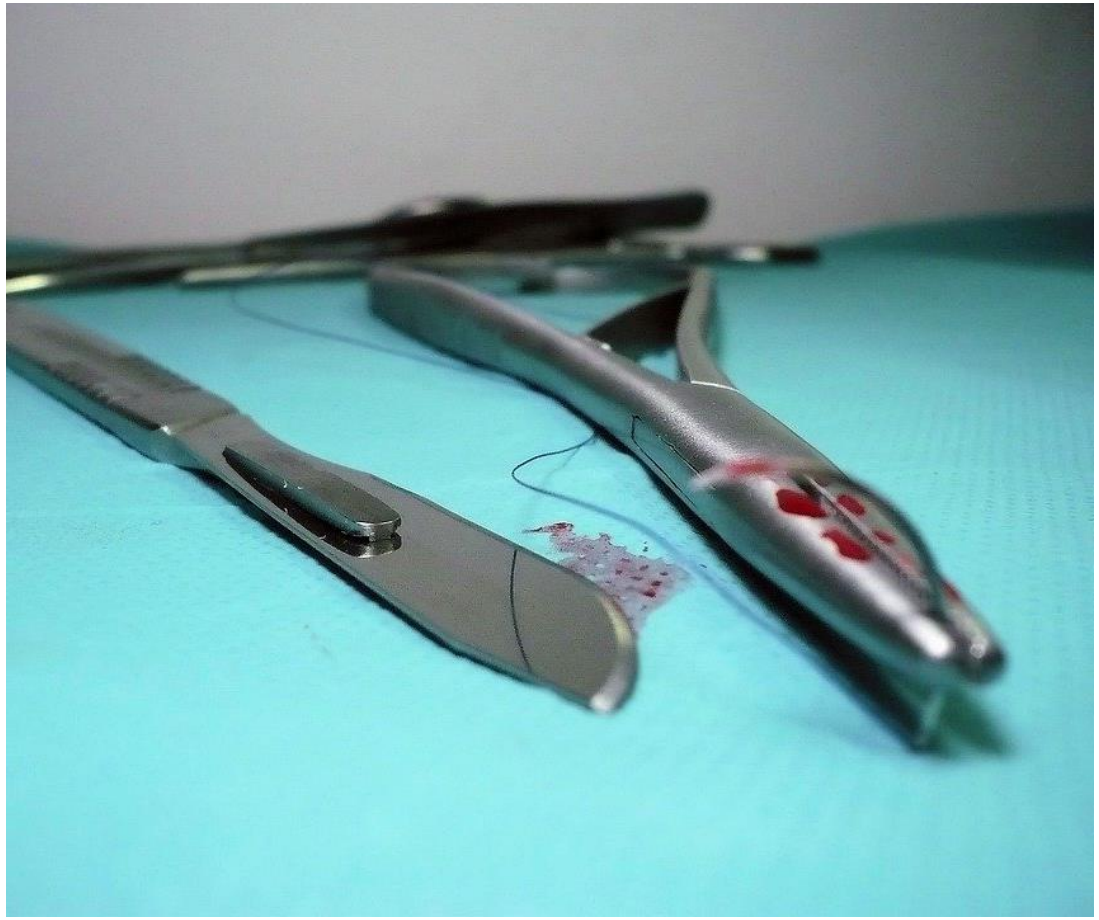
- Arguments why substitution not feasible

  Taking into account vulnerable groups

GSPR #10.4.1 – Example

Cobalt

- Present as impurity > 0.1% w/w in most stainless steels (such as 316L)
- “Harmonized classification as **Carcinogen Category 1B**, Mutagenic Category 2, Skin Sensitizer 1, Respiratory Sensitizer 1, **Reprotoxic 1B** and Aquatic Chronic 4”
- Must meet requirements in the MDR for **justification** of the presence AND specific **labelling** requirements (GSPR 10.4.5)



GSPR #12.. Incorporated substances

GSPR	Specifics	Comment
# 12.1	Requirement related to devices incorporating a substance considered to be a **medicinal product**.	Documentation - Quality, Safety, Usefulness Annex II 6.2 (a) in MDR and Annex I to Directive 2001/83/EC
# 12.2	” Devices that are composed of **substances** … **intended to be introduced** into the human body, and that are **absorbed by** or **locally dispersed** in the human body … evaluation of **absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction** …”	**ADME** – by literature if possible or toxicokinetic studies Interactions with substances/ materials Toxicokinetics only addressed in ISO 10993- 1:2018 (6.3.2.14) for resorbable devices

Substance based devices in ISO 10993?

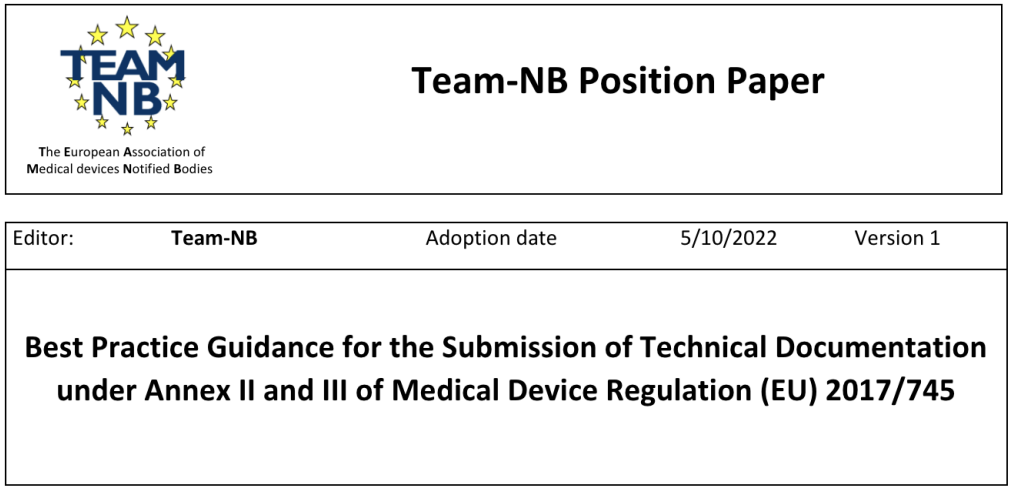
Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by		Endpoints of biological evaluation														
of body contact	Contact duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Contact: A – limited (≤24 h); B – prolonged (>24 h to 30 d); C – Long term (>30 d)																
Intact skin	A	X[g]	E[h]	E	E											
	B	X	E	E	E											
	C	X	E	E	E											

Where to find information

EU MDR – Biocompatibility

- The EU MDR – Open access
  - GSPR (Annex I)
  - Technical Documentation (Annex II)
  - Requirements for NB (Annex VII)



- ISO 10993 standard series and product specific standards

MDR - CMR and ED

- Annex I: General Safety and Performance Requirements
- Chapter II: Requirements regarding design and manufacture

- 10.4 Substances
- 23.1 Information on the label
- 23.4 Information in the instructions for use

EU MDR – CMR and ED

Summary of Classification and Labelling

Harmonised classification - Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

General Information

Index Number	EC / List no.	CAS Number	Inte
607-317-00-9	204-211-0	117-81-7	bis(2-ethylhexyl) phthalate di-(2-ethylhexyl) phthalate DEHP

ATP Inserted / Updated: CLP00

CLP Classification (Table 3)

Classification		Labelling		
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictogram C
Repr. 1B	H360FD	H360FD		GHS08 Dgr

https://echa.europa.eu/sv/information-on-chemicals/cl-inventory-database/-/discli/details/10536

Scientific Committee on Health, Environmental and Emerging Risks

SCHEER

GUIDELINES

on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties

Challenges, Experiences and Tips

— *Summary*

Notified bodies' expectations

- Chemical information with material assessments, including assessment of manufacturing aids
- ADME – clearly addressed with separate subheadings
- When testing is performed, clear connection to the test article
- Whole life-cycle of the MD being considered

Notified bodies' expectations, continued

- Structured assessment program with biological plan and report
- Record the rationale for selection, waiving or performing of tests – all applicable endpoints within the Table A.1

Specific questions from single NB

- CMR/ED also for primary packaging as being part of product - not limited to substance based
- Differences in interpretation of applicability of CMR/ED from the same NB
- Request of detailed prof of competence and sometimes to be certified toxicologist
- Tox assessment (by ERT) of material info for device with only potential indirect skin contact
- E/L testing of panel in clinical setting only touched by clinician with gloves

Further comments

- Acceptance of *in vitro* both from irritation and sensitization for intact skin (in some cases)

In summary

- Transparency and control
  - – quality, traceability, and competence of evaluator

- Risk-based approach and 3R
  - – justify testing

- Total life cycle and compatibility

- 10.4.1 CMR and ED substances in focus!

  > 0.1% w/w per device, part of, or material in the device

2024 Bi Biocompatibility Insights

Copenhagen, Oct 15-17

Veranex Biocompatibility Coffee Break

Lina.burman@veranex.com
Monica.grekula@veranex.com

Free discussion forum. To get an invitation, send an email to:
biocompatibility@veranex.com