Opportunities for 3Rs implementation in medical device testing

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Medical Device Development in Europe

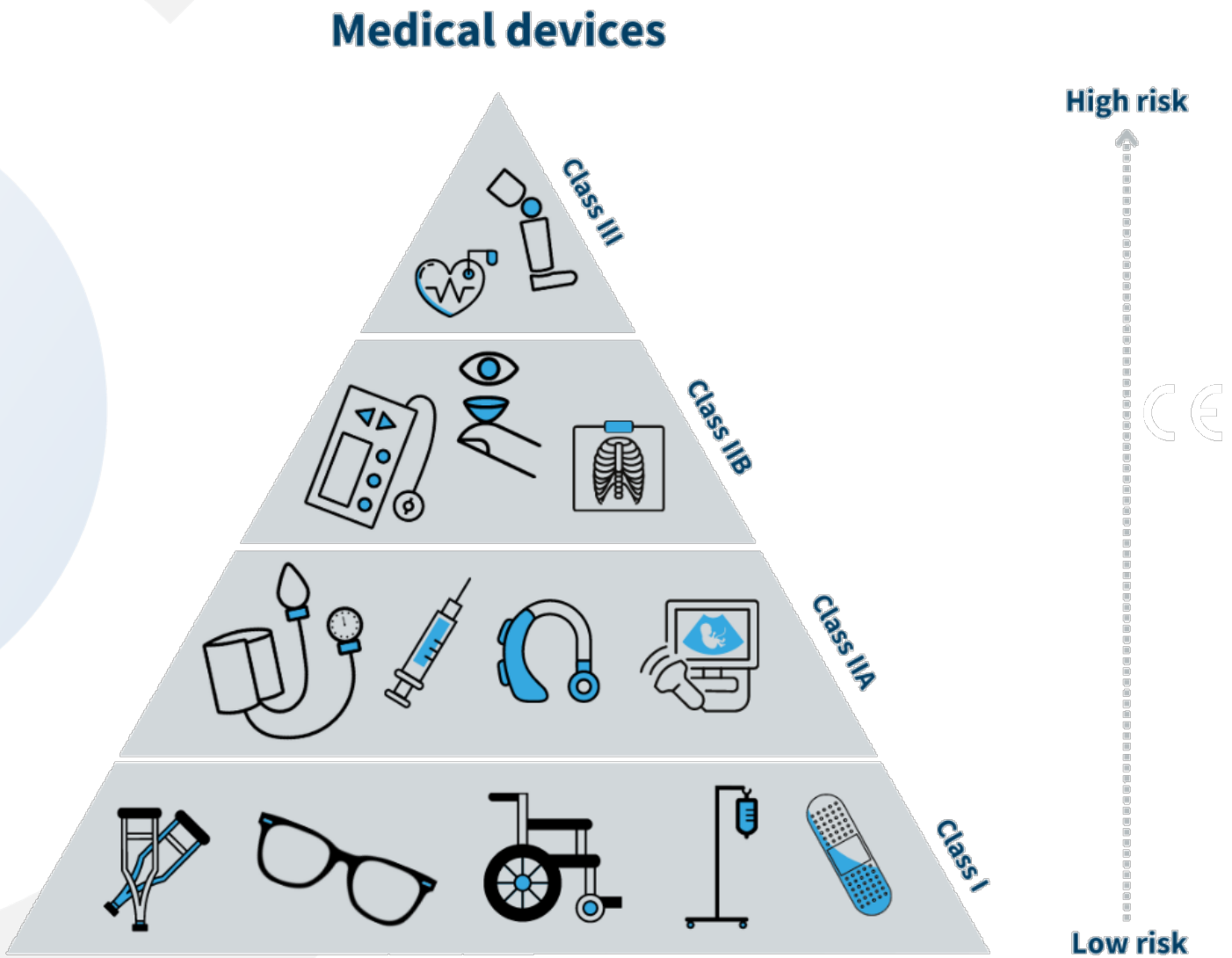

Illustration source: https://laegemiddelstyrelsen.dk/en/devices/

Medical Device Development in Europe

Notified Body
e.g. SGS
Self certification
(lowest risk
classes only)

Pre-clinical development

market
CE

Illustrations used: created by *amethyst studio* and *Gloria Maggioli*, downloaded from *the noun project*

Medical Device Development in Europe

Notified Body
e.g. SGS
Self certification
(lowest risk
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Pre-clinical development

Clinical Investigation

market
CE

National Competent Authority
e.g. FAMHP

Notified Body
e.g. SGS

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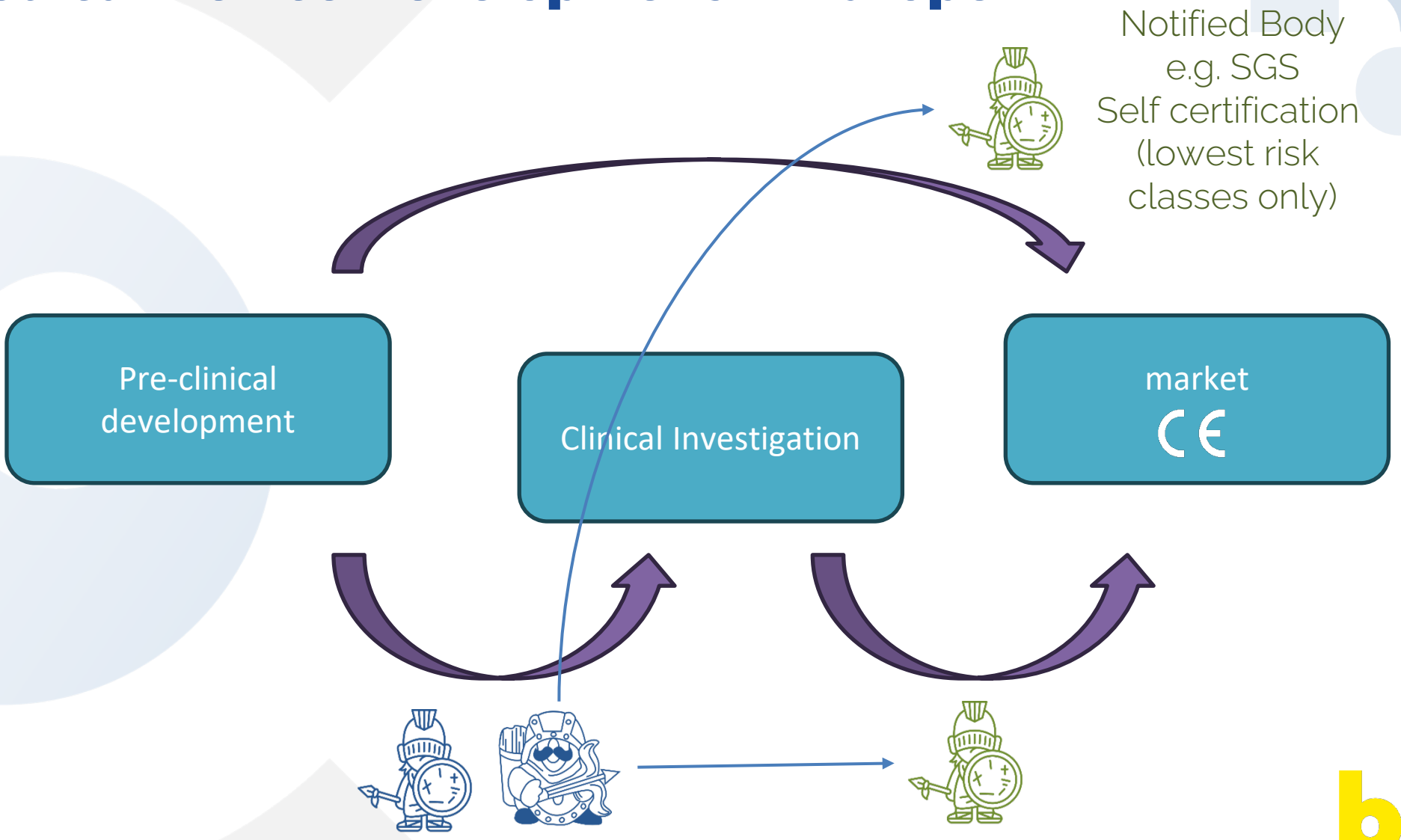
Medical Device Development in Europe



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Use of animal testing in medical device development

- Early development

  Highly variable, little guidance and information available

- Late development

  Acute and/or chronic safety and/or feasibility
  Some vertical standards are available
  Large animal models not uncommon

- Biological safety (biocompatibility)

  Horizontal standards (ISO 10993 series)
  (still) makes extensive use of small animal models

  E.g.: skin sensitization, skin irritation, eye irritation, acute toxicity, implantation, ..

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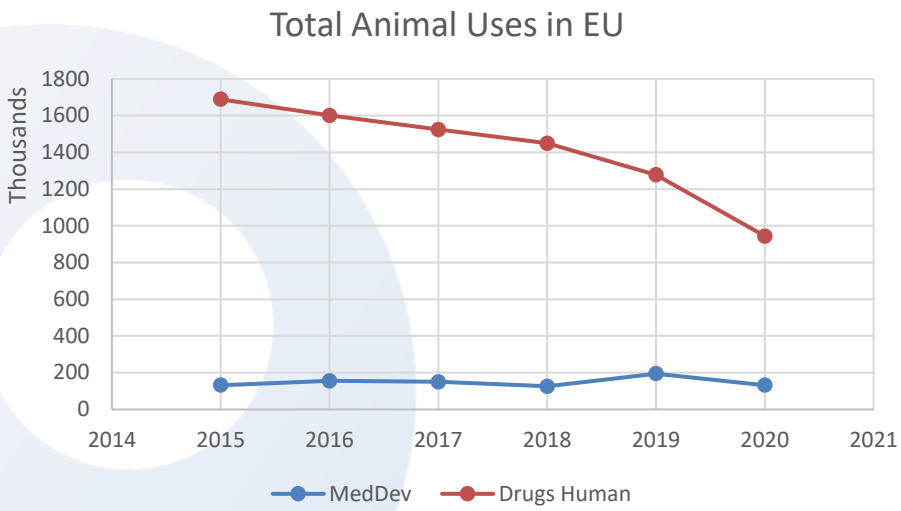
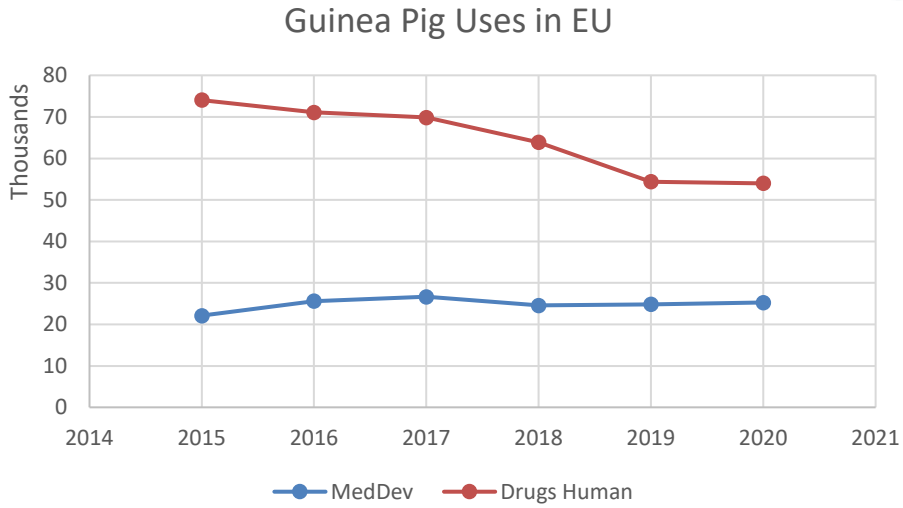
Animal testing and medical devices: European data





2020, medical devices, guinea pigs:
99.4% for skin sensitization testing

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Data source: ALURES – ANIMAL USE REPORTING - EU STATISTICS DATABASE ON THE USE OF ANIMALS FOR SCIENTIFIC PURPOSES UNDER DIRECTIVE 2010/63/EU

ISO 10993-10 (2010) sensitisation testing

In practice:

Mainly **Guinea Pig Maximization Test (GPMT)**; Closed-Patch (Buehler) test and murine Local Lymph Node Assay (LLNA) also in standard but used less.

Methods based on established **methods for sensitization testing of (specific, isolated) chemicals** but used with medical device **extracts** here

GPMT:
Induction phase 1 : intradermal injection, preferably at highest concentration causing some (up to moderate) erythema. Often simply undiluted extract.

Induction phase 2: 7 days later. topical induction using extract on patch. Same site. Occlusive dressing for 48 hours.

Challenge phase: 14 days later. Topical application (using patch) on previously untreated site; occlusive dressing for 24 hours.

Readout (24 & 48 hours): grading of skin reactions (redness, swelling) to assess sensitization

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Skin sensitisation testing – relevance?

MedTech Summit 2022, representative of large CRO:

"We started realizing that these old animal tests are really not very good. In fact, some of them are pretty bad, okay. So, I am not going to throw out any numbers because I do not want you guys to hate me. But I have been doing sensitisation tests for 20 years, ok? We do six to seven maximization tests a week. Each one of those tests we do anywhere between 30 to 45 guinea pigs per test. I have been doing that for twenty years. Do the math. Right.
Guess how many sensitisation tests I have failed in twenty years?

0.

Ok. So that gives you a sense how sensitive the sensitisation test is.."

The math: **0 out of ~ 240.500** [20 x 50 * 6.5 * 37 =]

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Skin sensitization and medical devices

So there are no medical devices with a skin sensitization potential on the market?

Well…

Figure 1: Mild allergic contact dermatitis caused by a previously applied IBOA-containing Freestyle® Libre glucose sensor.

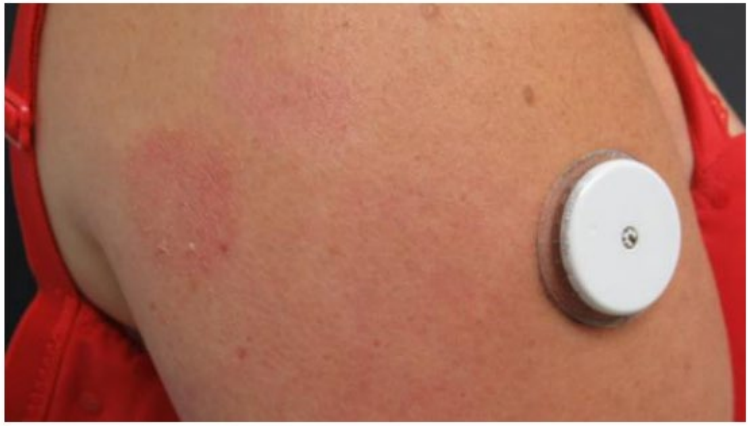
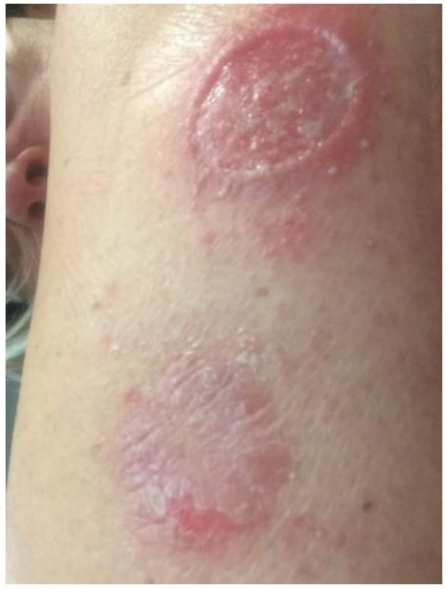


Figure 2: Severe allergic contact dermatitis caused by the IBOA-containing Freestyle® Libre glucose sensor; in this patient spontaneous detachment of the sensor frequently occurred.



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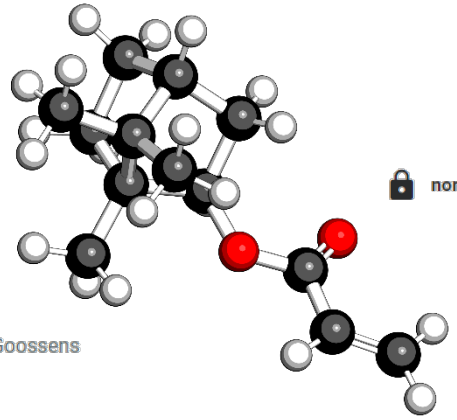


Dermatitis > VOL. 31, NO. 1 | Contact Allergen of the Year

normal

Isobornyl Acrylate

Olivier Aerts, Anne Herman, Martin Mowitz, Magnus Bruze, and An Goossens

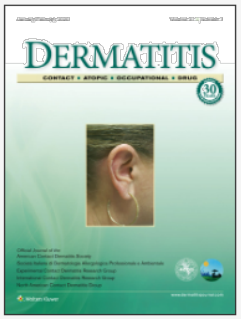
Published Online: 1 Feb 2020

Article Tools Title Share

Abstract

Multidisciplinary collaboration between several European dermatology departments has identified isobornyl acrylate (IBOA; CAS 5888-33-5), once deemed a low-risk sensitizer, as a major culprit contact allergen in glucose sensors and insulin pumps, medical devices used by diabetes patients worldwide. Although the patch test modalities of IBOA have been fairly well characterized, intriguing questions remain. For example, its cross-reactive profile to other acrylates remains to be determined, and the striking occurrence of concomitant positive patch test reactions to sesquiterpene lactones needs to be further elucidated. Importantly, the path to its discovery as a contact sensitizer in diabetes devices and the difficulties that were associated with this quest illustrate that apparent difficulties in obtaining sufficient cooperation from the medical device industry may seriously hamper the correct workup of cases of allergic contact dermatitis. The IBOA saga will convince companies to lend more cooperation to dermatologists and policymakers to side with patients and physicians when it comes to updating medical device regulations, including the compulsory labeling of medical devices in general and of diabetes devices in particular.

Figures References Related Details



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Information

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Skin sensitisation testing – what goes wrong

Use of **extracts**:

- sensitization tests originally **developed for single chemicals**, typically tested as dilution series
- for medical devices, extracts are made: for sensitization testing, this often involves a **saline and oil extract**.
- composition of extracts is not determined: we have no idea of exposure
- typically, **extraction solvents and conditions differ from those used for E&L testing**

Novel approach methodologies (NAM)?

Developed for chemicals; require adaptation and validation for medical devices

"*In 2024, Working Group 8 plans to begin preliminary work on a global round robin study of in vitro sensitization methods*"

"*Even though many in vivo tests have never formally been validated, regulators often prefer these established methods over newer, industry-developed in vitro alternatives.*"

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Kandárová H and Pôbiš P (2024), The "Big Three" in biocompatibility testing of medical devices: implementation of alternatives to animal experimentation—are we there yet? Front. Toxicol. 5:1337468. doi: 10.3389/ftox.2023.1337468

Skin sensitisation testing – legal basis

What does the law say?

Medical Device Regulation, 2017/745, General Safety and Performance Requirement N° 1:

"Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.
They shall besafe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art."

+ other GSPRs

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Skin sensitisation testing – legal basis

What does the law say?

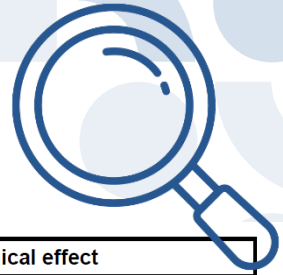
Medical Device Regulation article 8 (**use of harmonized standards**)

"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."

In other words: compliance with harmonized standards is **one way** to demonstrate conformity with the requirements of the medical device regulation.

No legal obligation to adhere to standards, including ISO 10993

The old checkbox approach: ISO-10993-1 (2009)



NBN EN ISO 10993-1 (2009) ISO 10993-1:2009(E)

Annex A
(informative)

Biological evaluation tests

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device	Skin	A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (≤ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
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	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					

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Skin sensitisation testing – standards

What do the standards say?

ISO 10993-1:2018 Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

Evaluation can include both a review of relevant existing preclinical and clinical data and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the medical device under design.

[…]

Test results cannot guarantee freedom from potential biological hazards, thus biological investigations shall be followed by careful observations for unexpected adverse reactions or events in humans during clinical use of the medical device.

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Animal testing in Medical Device Development: purpose

What do the standards say?

ISO 10993-1:2018 Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process

In vitro test methods, which are appropriately validated, reasonably and practically available, reliable and reproducible, shall be considered for use in preference to in vivo tests (see ISO 10993-2)

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The way forward

In many cases, **weight of evidence** of

- clinical use of similar materials
- chemical and physical characterization of device
- toxicological evaluation based on E&L testing/material data
- potentially *in vitro* sensitization testing

Will be **enough to conclude that there is no significant safety data gap that would justify *in vivo* testing**

Future **update of 10993-1**: principle of "**biological equivalence**"

Consider **integration of endpoints** in already planned studies, e.g. acute toxicity and local effects of implantation in already planned safety & feasibility studies, rather than as separate, "modular" studies

Need for **regulatory harmonization**: complex landscape (NCA, NB, FDA, ISO ..)

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