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Engineering the extraordinary

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ASCCT-ESTIV Webinar

NAMs & Medical Devices: Challenges and Successes

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LEGAL DISCLAIMER

This presentation reflects the opinions of the presenter not those of Medtronic plc.

The presenter has no conflicts of interest.

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OUTLINE

- Background
- In Vitro Irritation Testing
- In Vitro Sensitization Testing
- Pyrogenicity Testing

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BACKGROUND

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NEW APPROACH METHODOLOGIES (NAMs)

Are innovative, non-animal testing strategies—including **in vitro assays**, **in chemico methods**, **in silico computational models**, **organoids**, and microphysiological systems (**organ-on-chip**)—being developed to supplement or replace testing in support of **Replacement, and Refinement.**

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CHANGING REGULATORY LANDSCAPE

ALTEX
ALTERNATIVES TO ANIMAL EXPERIMENTATION

Comment

The Turning Point: April 2025 Marks Historic Shift in US Animal Testing Policy

Thomas Hartung[1,2]

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doi:10.14573/altex.2504301

Recent developments in the United States mark a significant turning point in the global transition away from animal testing toward more human-relevant approaches in biomedical research and regulatory science. In April 2025, we witnessed a remarkable synchronicity of policy initiatives across major US regulatory agencies, namely FDA, EPA and NIH, that signals a paradigm shift in how we approach safety testing and biomedical research.

The United States takes decisive action

On April 10, 2025, FDA Commissioner Martin A. Makary unveiled an ambitious roadmap aimed at rapidly reducing animal testing in preclinical safety assessments[1]. This decisive action recognizes the significant limitations of animal models, highlighted by compelling statistics showing that more than 90% of

ological systems (MPS), computational modeling, and advanced human-based *in vitro* assays. These technologies not only promise enhanced predictability regarding human responses but also significantly mitigate the ethical dilemmas inherent in animal experimentation.

Microphysiological systems, in particular, stand at the forefront of this scientific revolution (Hartung and Smirnova, 2025). By combining microfabrication techniques with modern tissue engineering, these technologies offer new *in vitro* approaches to drug screening by mimicking the complicated mechanical and biochemical behaviors of human organs.

The MPS World Summit: A critical platform for progress

As these regulatory shifts accelerate the adoption of human-rele-

Vol 42, No 3 (2025)

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FDA DEVELOPMENTS (2025)

On April 10, 2025, FDA announced its plan to **phase out its animal testing** requirement for drugs.

- **Immediate Implementation:** Encourage use of NAMs, such as AI models, in vitro assays, organ-on-a-chip systems, and human cell or tissue assays.
- **Reduction & Replacement:** Animal testing requirements will be reduced, refined, or potentially replaced using these more effective, human-relevant methods.
- **Collaborative Efforts:** FDA will work with agencies, NIH, and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to validate and promote NAMs.

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UK’S PHASE-OUT ROADMAP (2025)

On November 11, 2025 a **phase-out roadmap, not an outright ban** was announced that set replacement milestones while continuing to allow animal use where validated alternatives don't yet exist.

By end of	Milestone
2025	Rabbit pyrogen test eliminated, replaced by the in-vitro Monocyte Activation Test (MAT).
2026	Skin irritation, eye irritation/corrosion, and skin sensitization tests ended. UK Centre for the Validation of Alternative Methods (UKCVAM) established
2027	Replace mouse botulinum toxin test with DNA-based methods for contamination testing of human medicines.
2030	Significantly reduce in vivo ADME studies in dogs and non-human primates, with an overall target of reducing use in human-medicine trials by at least 35%.
2026 – 2035	Accelerate broader adoption of non-animal techniques across the research base.

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EU’S PHASE-OUT ROADMAP (2026)

Adoption: On June 1, 2026, the Commission adopted the roadmap for a **gradual—not immediate**—phase-out of animal testing in chemical safety assessments.

Scope: 22 actions across three pillars, covering 15 legislative domains including **medical device biocompatibility**.

Medical devices: Addressed via chemical/material safety; **skin sensitization** (ISO 10993-10) targeted for full replacement, potentially by 2029.

Long-term ambition: A paradigm shift toward a **Next-Generation Risk Assessment** framework, with a 2029 stock-taking conference.

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IN VITRO IRRITATION TESTING

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MEDICAL DEVICE TOX TESTING

ISO 10993 Standards

A series of global standards for evaluating the **biocompatibility** of a **medical device** prior to **clinical study**.

Toxicology tests

- ✓ Cytotoxicity
- ✓ Irritation
- ✓ Sensitization
- ✓ Acute Systemic
- ✓ Subchronic
- ✓ Genotoxicity
- ✓ Pyrogenicity
- ❖ Chronic
- ❖ Reproductive/Developmental
- ❖ Carcinogenicity

✓ required

❖ rarely run

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IN VITRO SIX PACK FOR MEDICAL DEVICES

Current In Vivo Method	In Vitro Replacements
Irritation (rabbits)	ISO 10993-23:2021 3-D human skin assays
Sensitization (guinea pigs)	OECD 442 Battery (2 of 3) Genomic Assays (GARD & SENS-IS)
Acute systemic toxicity (mice)	OPERA/CATMoS, NICEATM Data mining
Thrombogenicity (dogs)	Human Blood-Based Assays Chandler Loop, Vacutainer Tubes
Hemolysis (rabbit blood)	Human blood round robin
Pyrogenicity (rabbits)	Monocyte Activation Test (MAT)

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TIMELINE

2010 – ISO/TC 194 Meeting in Berlin

2011 – Research Begins at Medtronic

2012 – Pilot Project Completed

2017 – Round Robin Study Completed

2019 – Follow-Up Study Completed

2021 – ISO 10993-23 Published

2025 – ISO 10993-23/Amd 1 Published

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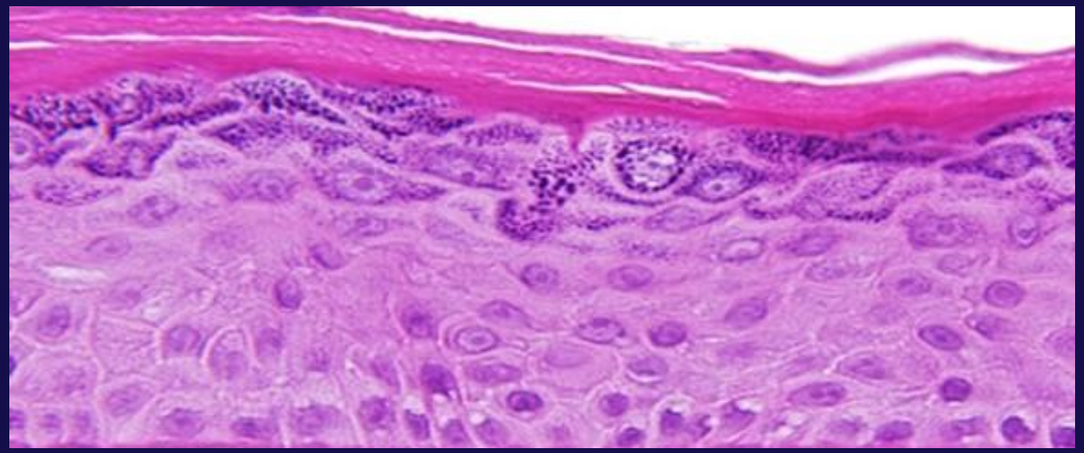
ROUND ROBIN STUDY (2013-2017)

- ISO/TC 194 Working Group 8 Task Force
- 24 laboratories around the world
- 2,000 blinded polymer samples
- Tissues: EpiDerm™ & SkinEthic™ RHE



EpiDerm™, MatTek Life Sciences

- Results published in a special issue of *Toxicology In Vitro* (TIV, 2018)

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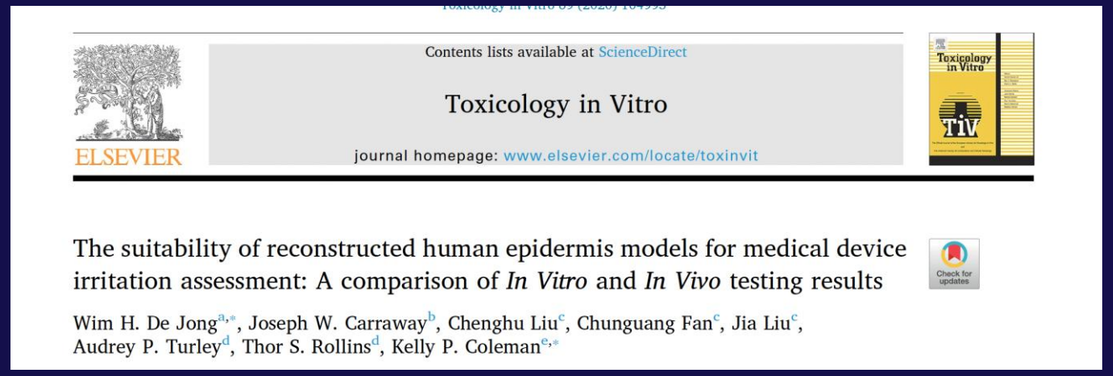
COMPARISON OF IN VITRO AND IN VIVO RESULTS (2020)



Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

The suitability of reconstructed human epidermis models for medical device irritation assessment: A comparison of *In Vitro* and *In Vivo* testing results

Wim H. De Jong[a,*], Joseph W. Carraway[b], Chenghu Liu[c], Chunguang Fan[c], Jia Liu[c], Audrey P. Turley[d], Thor S. Rollins[d], Kelly P. Coleman[e,*]

RhE in vitro models produced results essentially equivalent to the in vivo rabbit intra-cutaneous test, making them acceptable replacements for medical device irritation.

The rabbit intracutaneous test was more sensitive at detecting irritant activity than the rabbit skin patch test—shown here for the first time for both chemicals and device extracts.

45 marketed orthopedic devices scored non-irritant in both RhE and rabbit intracutaneous tests, confirming strong in vitro/in vivo concordance.

Most spiked positive-control polymers performed as expected, though silicone-HA gave inconsistent results due to inhomogeneous irritant distribution.

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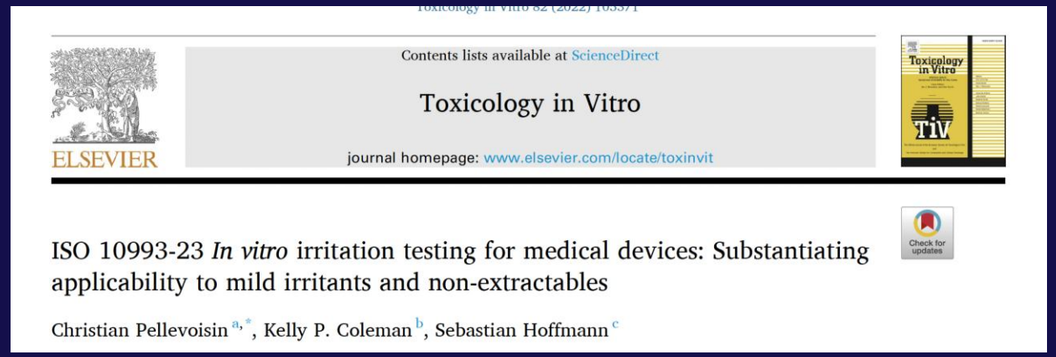
IN VITRO IRRITATION TESTING OF MILD IRRITANTS (2022)



Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

ISO 10993-23 *In vitro* irritation testing for medical devices: Substantiating applicability to mild irritants and non-extractables

Christian Pellevoisin [a,*], Kelly P. Coleman [b], Sebastian Hoffmann [c]

The RhE-based ISO 10993-23 protocol reliably detected mild irritants (GHS Category 3) in spiked medical device extracts, even at concentrations as low as 1%, classifying 7 of 9 tested mild irritants as irritants.

The ISO protocol is more sensitive than the OECD TG 439 chemical protocol—due to higher applied dose (100 µL vs. 16 µL) and longer exposure (24 h vs. 42 min)—detecting irritants in complex extracts that TG 439 missed.

RhE-based testing is readily applicable to non-extractable devices (creams, gels, sprays, fillers), detecting low spiked concentrations of strong (0.5–1%) and mild (1.5–10%) irritants applied directly to the tissue.

The method's high sensitivity strengthens patient safety; while it may occasionally yield false positives, this errs on the protective side for patients.

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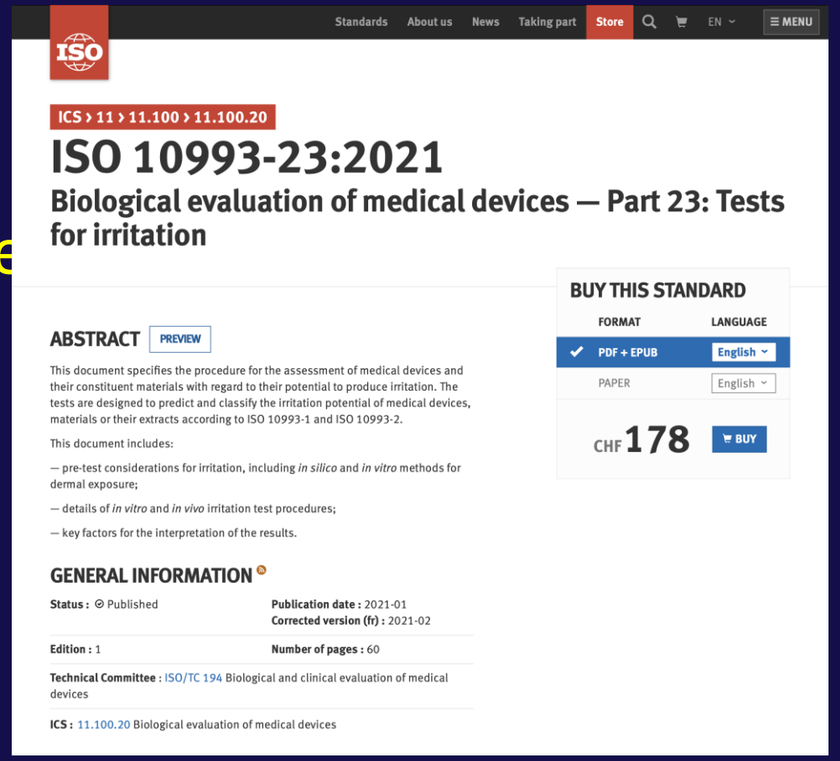
KEY CHANGES IN ISO 10993-23:2021

- **Clause 1**. Scope includes in vitro testing.
- **Clause 4.** "In vitro irritation test **shall** be performed before animal testing or human patch test is considered."
- **May 2025:** Amended to include Korea's KeraSkin and Japan's Labcyte tissues.



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GLOBAL ACCEPTANCE (OCTOBER 2025)

- 191 of the UN's 193 Member States (99%) directly or indirectly recognize ISO 10993-23 and accept in vitro irritation data.
- 95% of humanity lives in those 191 countries.
- Recognition by the US and Canada is pending.

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IN VITRO SENSITIZATION TESTING

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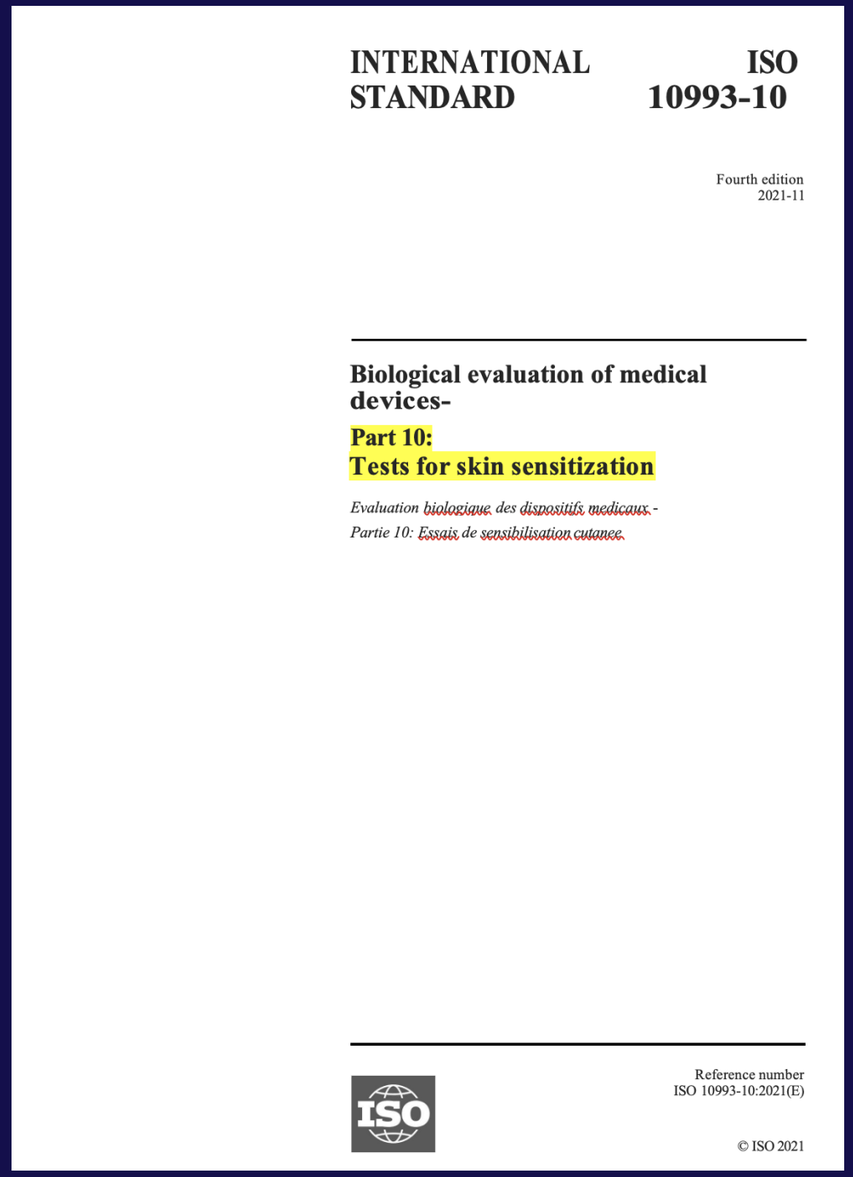
ISO 10993-10:2021
Tests for skin sensitization



INTERNATIONAL STANDARD ISO 10993-10

Fourth edition
2021-11

Biological evaluation of medical devices-

Part 10:
Tests for skin sensitization

Evaluation biologique des dispositifs medicaux -
Partie 10: Essais de sensibilisation cutanee

Reference number
ISO 10993-10:2021(E)

© ISO 2021

4 General principles - Step-wise approach

The available methods for testing sensitization were developed specifically to detect skin sensitization potential. Other types of adverse effects are generally not predicted by these tests.

This document requires a step-wise approach, considering that any stage can result in the conclusion that further testing for skin sensitization is not necessary:

a) literature and supplier information review, including chemical and physical properties, and information on the skin sensitization potential of any medical device constituent as well as structurally-related chemicals and materials; refer to ISO 10993-1 for details; conduct risk assessment based on existing information to determine whether skin sensitization risk is acceptable or whether further testing is necessary;

b) additional characterization and risk assessment, if needed, of the device material, involving chemical characterization and analysis of the test sample according to the general principles described in ISO 10993-18;

c) in vitro tests shall be considered in preference to in vivo tests in accordance with ISO 10993-2, and the replacement of the latter as new in vitro tests are scientifically validated and become reasonably and practicably available;

d) in vivo animal tests are only appropriate when test materials cannot be characterized and risk assessments cannot be undertaken using information obtained by the means set out in a), b) and c).

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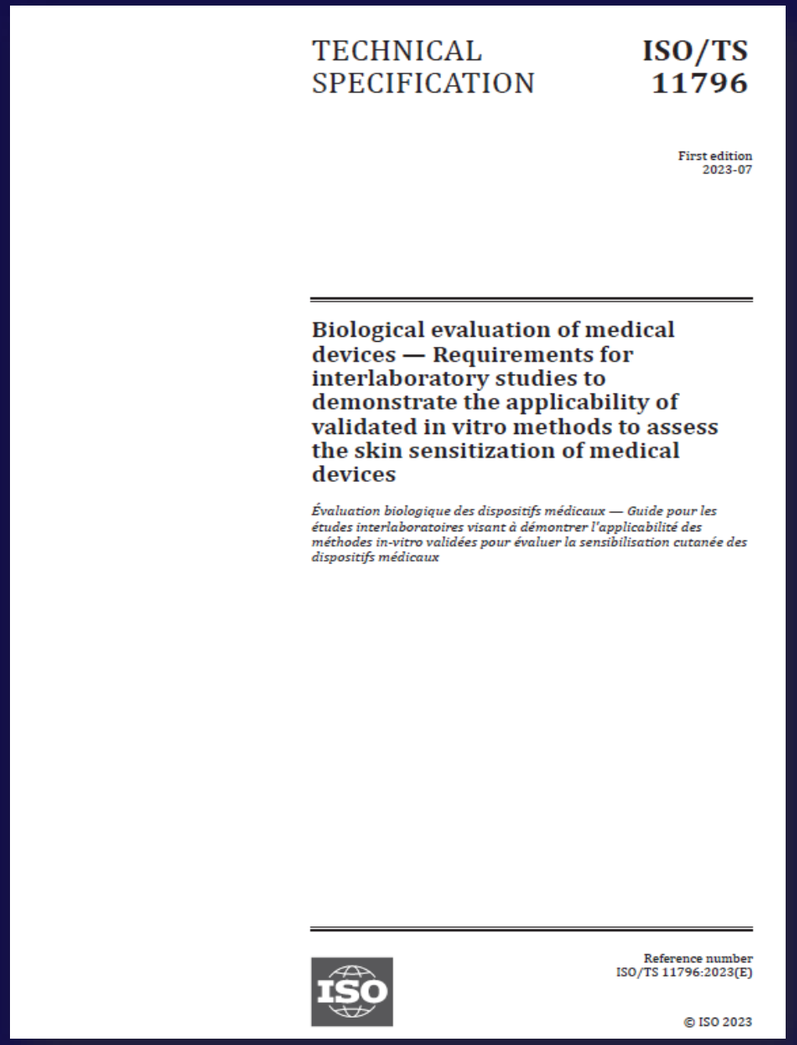
IN VITRO VALIDATION STUDY



TECHNICAL SPECIFICATION

ISO/TS 11796

First edition
2023-07

Biological evaluation of medical devices — Requirements for interlaboratory studies to demonstrate the applicability of validated in vitro methods to assess the skin sensitization of medical devices

Évaluation biologique des dispositifs médicaux — Guide pour les études interlaboratoires visant à démontrer l'applicabilité des méthodes in-vitro validées pour évaluer la sensibilisation cutanée des dispositifs médicaux

ISO

Reference number
ISO/TS 11796:2023(E)

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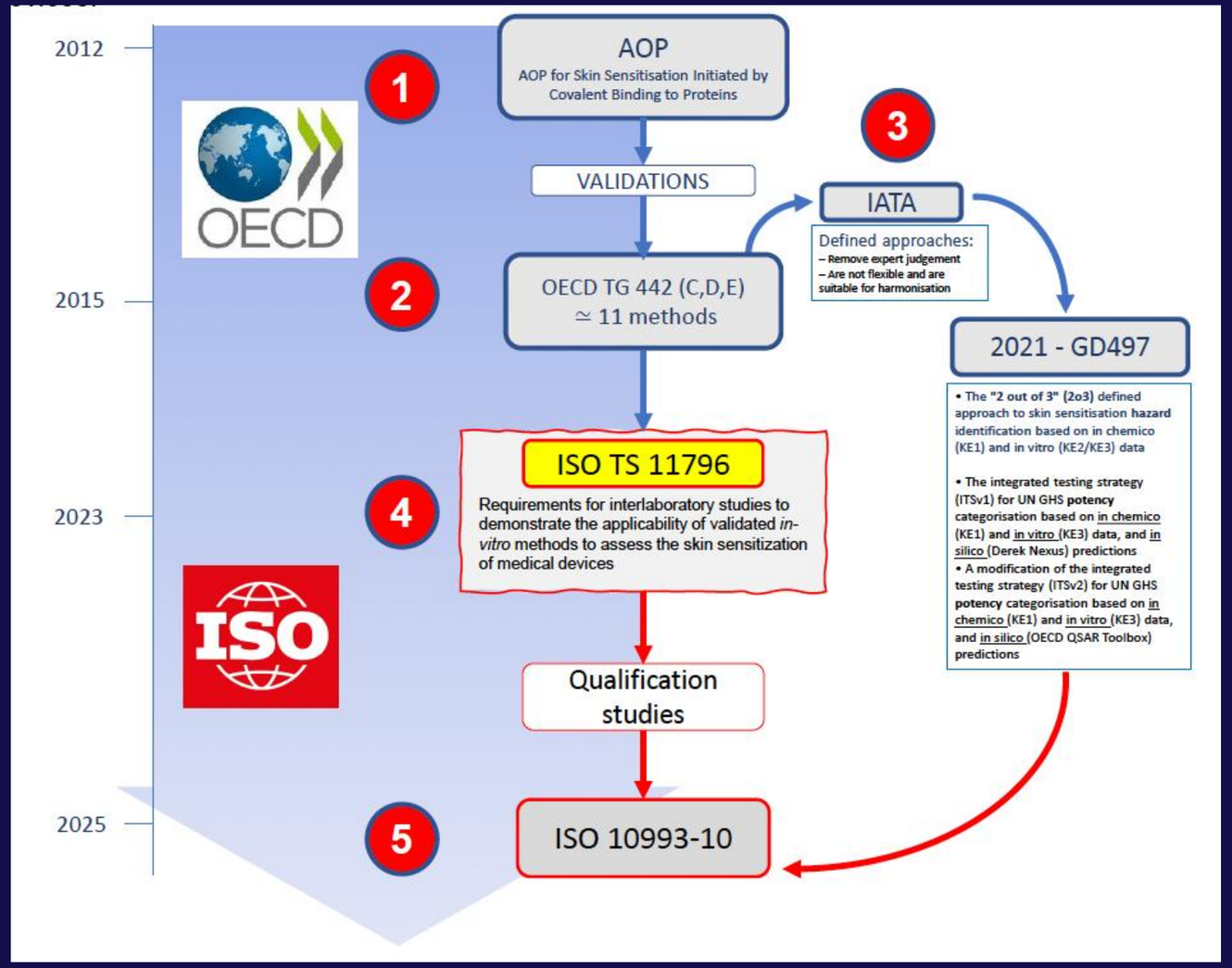

Source: Pellevoison et al., 2023

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SELECTED ASSAYS

ASSAY	KEY EVENTS	OECD GD	COMMENTS
GARD MD SenzaGen Sweden (200 genes)	3	442E	Also addresses Key Event 2
SENS-IS ImmunoSearch France (64 genes)	1, 2, 3	Pending	Works with SkinEthic and EpiDerm tissues
EpiSensA Kao Corporation Japan (4 genes)	2	442D	Epi2SensA works with EpiDerm tissues

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HAZARD IDENTIFICATION ACCURACY*

ASSAY	SENSITIVITY (%)	SPECIFICITY (%)	ACCURACY (%)
GARD^	92.7	96.0	93.8
SENS-IS**	95.8	96.5	96.0
EpiSensA†	92.6	63.0	82.7

*Compared to human data

^Johansson et al., 2019
**Cottrez et al., 2016
†Mizumachi et al., 2024

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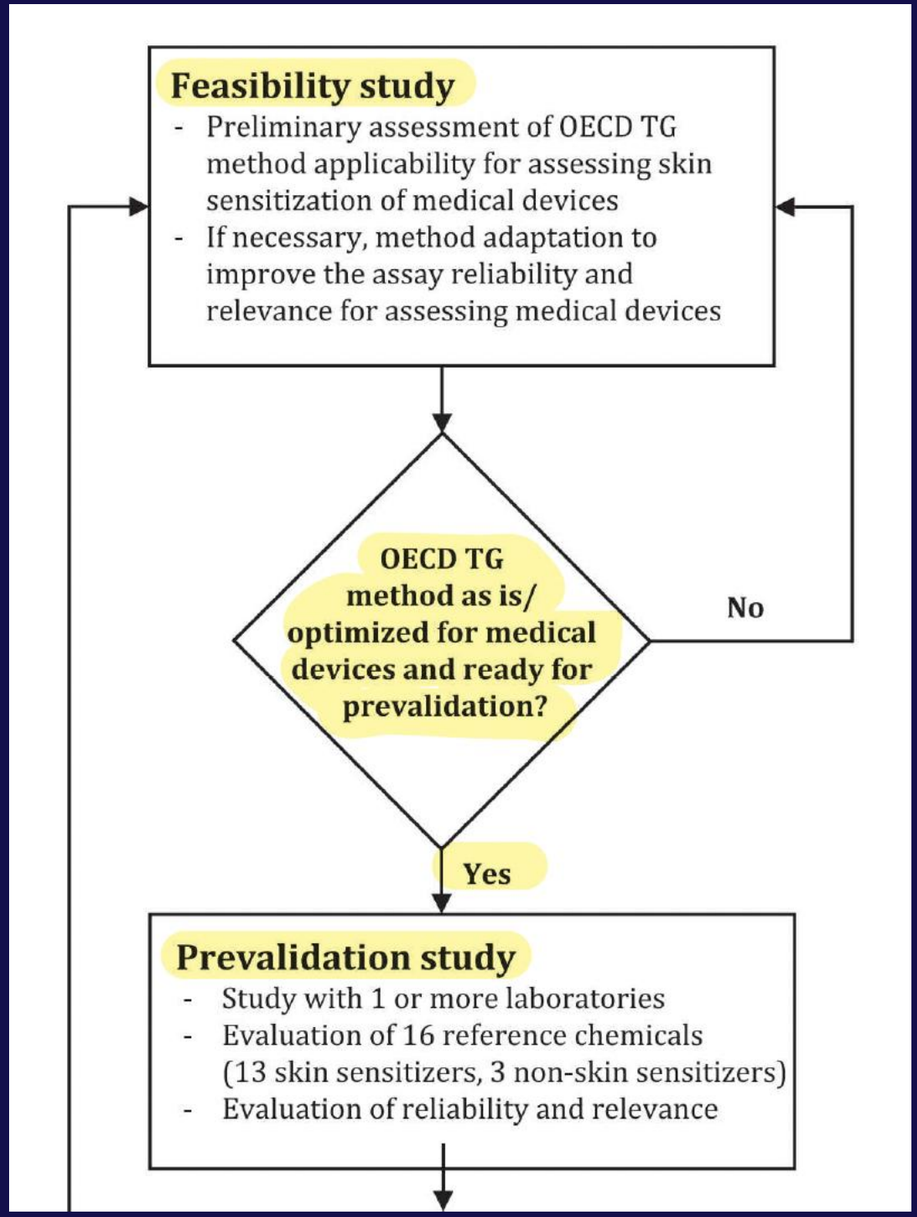
PROCESS STATUS

- ✓ **Feasibility studies – completed**
- ✓ **Pre-validation studies – completed**
- ✓ **Validation study – begins 2026**



Source: ISO/TS 11796:2023

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PREVALIDATION STUDIES

ASSAY	COMMENTS
GardSkin MD	Preliminary results very promising regarding the assay's ability to perform equivalent to, or better than, in vivo models.
Epi2SensA	The very high concentrations for certain weak sensitizers raises doubts about their relevance to the study of medical device extracts.
SENS-IS	In July of 2024, OECD issued a SENS-IS Draft Test 442 Guideline for Toxicogenomic Analysis of RhE Tissues for Skin Sensitization

Source: Minutes of the ISO/TC-194/WG8 meeting October 23-24, 202 - Paris, France

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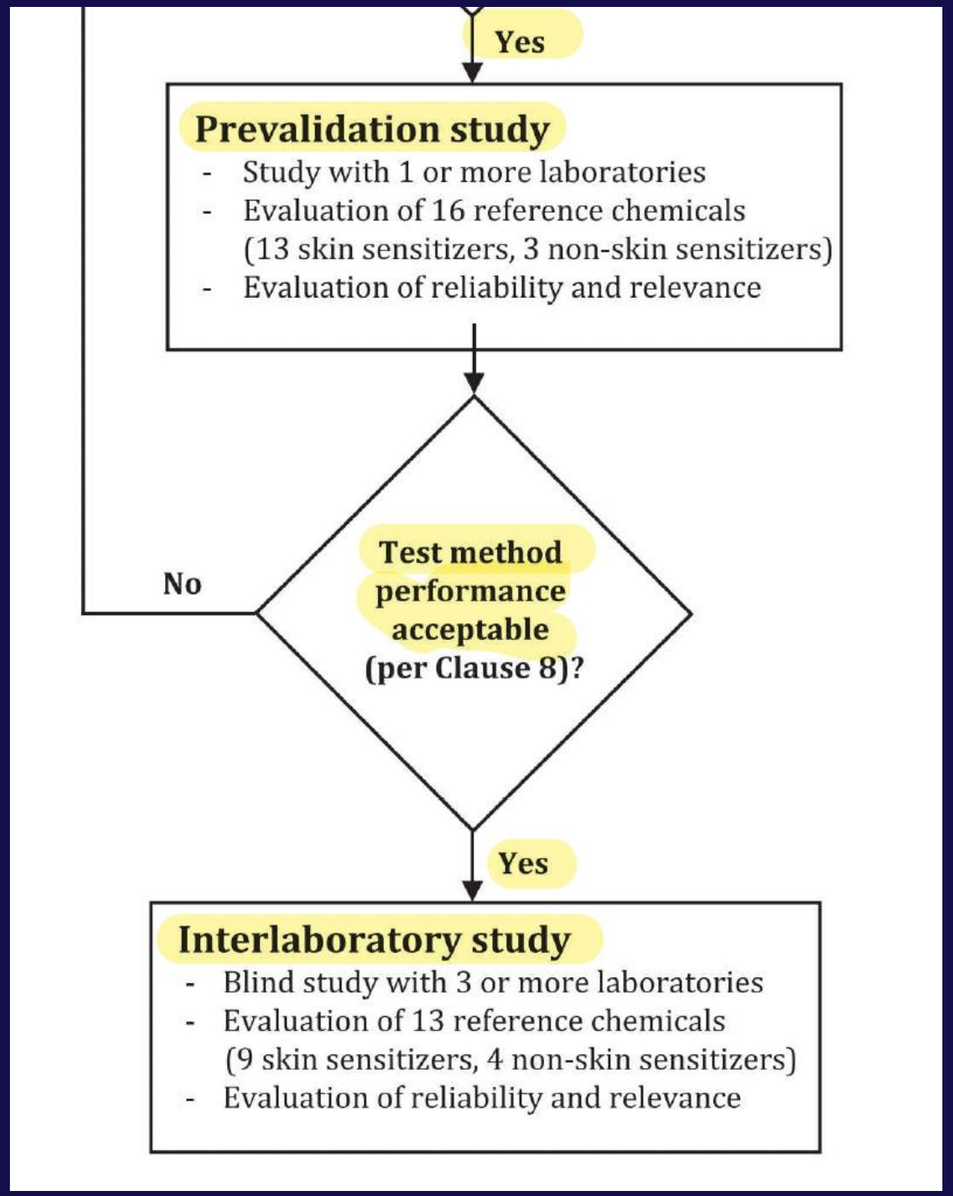
GLOBAL VALIDATION STUDY

- ✓ Three or more labs/assay
- ✓ Blinded study
- ✓ Sensitizers & non-sensitizers
- ✓ Reliability & relevance



Source: ISO/TS 11796:2023

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IN VITRO SENSITIZATION STUDY PHASES

Phase I – GARD Assay (2026) – Key Event 3

Phase II – EPI2-SenseA Assay (2027) – Key Event 2

Phase III – DPRA or SENS-IS (2028) – Key Event 1

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PYROGENICITY TESTING

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PYROGEN TESTING STANDARDS & GUIDANCE

- ISO 10993-1:2025 – Risk Management Process
- **ISO 10993-11:2017 – Systemic Toxicity: Annex G**
- ISO/TR 21582:2021 – Med. Device Pyrogen Testing
- FDA Use of International Standard ISO 10993-1
- FDA Guidance for Pyrogen and Endotoxin Testing

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ANNEX G MATERIAL-MEDIATED PYROGENS

Category	Substances
Cytokines	IL-1, TNF-α, IL-6, INF-γ
Prostaglandins	Prostaglandin E2
Neurotransmitters	Serotonin, Noradrenaline
Inducers	Polyadenylic, -uridylic, -bionosinic, -ribocytidylic acids
T.R. Center Disruptors	LSD, Cocaine, Morphine
O.P. Uncouplers	Picric acid, 4,6-Dinitro-o-cresol, 2,4-Dinitrophenol
Naphthylamines	N-Phenyl-2-naphthylamine, 1-Naphthylamine
Bacterial Exotoxins	TSST-1, SEA, SpeF, SpeC, botulism, diphtheria, tetanus
Metals	Nickel salts
Nanomaterials	Nanoparticles

Biological pyrogens, chemical pyrogens, drug pyrogens and uncouplers of O.P.

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ALTEX
ALTERNATIVES TO ANIMAL EXPERIMENTATION

ALTEX, accepted manuscript
published July 9, 2025
doi:10.14573/altex.2504231

Review Article

Material-Mediated Pyrogens in Medical Devices: Myth or Reality?

Lindsey K. Borton[1] *and Kelly P. Coleman*[2]
[1]Gradient, Boston, MA, USA; [2]Medtronic, Minneapolis, MN, USA

Abstract

Annex G of ISO 10993-11:2017 lists 24 substances that are allegedly material-mediated pyrogens (MMPs) in medical devices and recommends using the rabbit pyrogen test (RPT) for MMP evaluation. We aimed to establish whether medical devices contain MMPs; determine if MMPs are pyrogens or uncouplers of oxidative phosphorylation (UOPs); complete a survey of RPT failures; and develop a UOP screening list. A literature search was conducted to identify MMPs associated with medical devices. Concurrently, data mining was conducted to search for MMPs in medical device extractables databases and collect RPT data from industry and contract research labs. The literature search produced the conclusions: (1) Annex G's endogenous biological compounds are pyrogenic; (2) Annex G's drugs and UOP substances are not pyrogenic but thermogenic; (3) numerous other UOPs were identified; and (4) nearly all UOPs are poorly soluble in saline (the RPT's injection solvent). The data mining found two Annex G MMPs in medical device extracts that were not pyrogenic and confirmed that the RPT failure rate was low, with investigated failures caused by endotoxin or test incompatibilities, not by Annex G MMPs. Since no pyrogenic Annex G MMPs or saline soluble UOPs were found in medical device extracts, the RPT is unnecessary. If UOPs are detected during chemical characterization studies, an ISO 10993-17:2023 toxicological risk assessment can be used to determine their hazard potential. Residual biological contamination can be evaluated with the human monocyte activation test, which detects all biological pyrogens. The term "MMP" is inaccurate and obsolete.

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BORTON & COLEMAN RECOMMENDATIONS

Replace the RPT with modern human-relevant and chemistry-based methods and revise the standard.

- ✓ Use the human monocyte activation test (**MAT**) because it can detect all biological pyrogens.
- ✓ Use **ISO 10993-17:2023** toxicological risk assessment (paired with chemical characterization) to detected UOPs/thermogens.
- ✓ The term "material-mediated pyrogen" is **scientifically baseless** and should be retired in favor of "biological pyrogen" and "chemical thermogen."

PYROGEN TESTS COMPARED

Test Criteria	Rabbit Pyrogen Test	Monocyte Activation Test
Human specific	✗	✓
Detects endotoxins	✓	✓
Detects non-endotoxins	✓	✓
Lower Limit of Detection (EU/mL)	0.5*	0.1 – 0.004*
Low susceptibility to interfering factors	✓	✓
Delivers quantifiable results	✗	✓
Proficient in testing biologics	✓	✓
Avoids animal suffering	✗	✓
In vitro assay	✗	✓

Source: MAT-BIOTECH.COM

*Equal to 0.5 ng/mL

*Equal to 0.004 ng/mL

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MAT VERIFICATION

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MAT “VALIDATION” FOR MEDICAL DEVICES

FDA and ISO language about **“validating”** the MAT for medical devices concerns **method suitability** and **product-specific performance**, not about re-proving that MAT works as a pyrogen test in general.

The MAT’s 30-year history means **“assay validation”** at the platform level—fitness to detect pyrogens —is already done and recognized. Calling for another de novo **“validation of the MAT for medical devices” conflates assay validation** with **context-of-use** implementation.

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MAT “VALIDATION” SUMMARY

Insisting that the **“MAT must be validated for medical devices”** reads as a legacy formulation from an era when regulators were still treating devices as a special pyrogenicity case.

The current evidence and standards instead support a framework in which the MAT is a **fully validated pyrogen test**, and device manufacturers perform **product specific method verification** to show suitability for their particular device and extraction scheme.

Hartung, 2021, 2026; FDA, 2026

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VERFICATION DEFINITION FROM USP <1226>

- ✓ Method verification is **“an assessment whether a compendial method is suitable under actual conditions of use.”**
- ✓ It is required the first time a lab uses a compendial procedure for a given **sample type;** it is both **lab-specific** and **matrix-specific**.
- ✓ A **new sample** type or a **new lab** triggers a new verification, even if the procedure and product class are unchanged.
- ✓ Verification strategies can vary, but determination of **specificity** for the actual sample (checking for interferences) is always required.

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NAMs SUMMARY

- ✓ Acceptance of NAMs continues to grow.
- ✓ Major geographies support them.
- ✓ In vitro irritation testing for medical devices is accepted by 99% of world governments.
- ✓ The in vitro sensitization validation has begun.
- ✓ The RPT has been dropped from ISO 10993-1 and ISO 10993-11 is being amended.

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