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Engineering the extraordinary

Toxicological Risk Assessment of Medical Devices: ISO 10993 Updates

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MedCon Conference

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LEGAL DISCLAIMER

The presenter has no conflicts of interest.

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

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OUTLINE

1. Toxicological Risk Assessment
   ISO/FDIS 10993-17:2023

2. Update on In Vitro Irritation
   ISO 10993-21:2021

3. References

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TOXICOLOGICAL RISK ASSESSMENT

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TIMELINE

- 1976 – Medical Device Amendments to the FD&C Act
- 1986 – Tripartite Biocompatibility Guidance, G87-1
- 1995 – Use of ISO 10993-1, FDA Guidance, G95-1
- 2002 – ISO 10993-17: Allowable Limits for Leachables
- 2019 – ISO/TS 21726: Application of TTC
- 2020 – Use of ISO 10993-1:2018, FDA Guidance
- 2020 – ISO 10993-18: Chemical Characterization
- 2023 – ISO 10993-17: Toxicological Risk Assessment

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ISO 10993-17:2002

Methods for the Establishment of Allowable Limits for Leachable Substances

- 2nd Oldest ISO 10993 Standard
  - ✓ 10 clauses, 4 Annexes, 33 Pages
- Parameters:
  - ✓ Tolerable Intake (TI)
  - ✓ Tolerable Exposure (TE)
  - ✓ Tolerable Contact Level (TCL)
  - ✓ Modifying Factors (MF)
  - ✓ Uncertainty Factors (UF)
  - ✓ Allowable Limits (AL)
- Didn't explain tox risk assessment!

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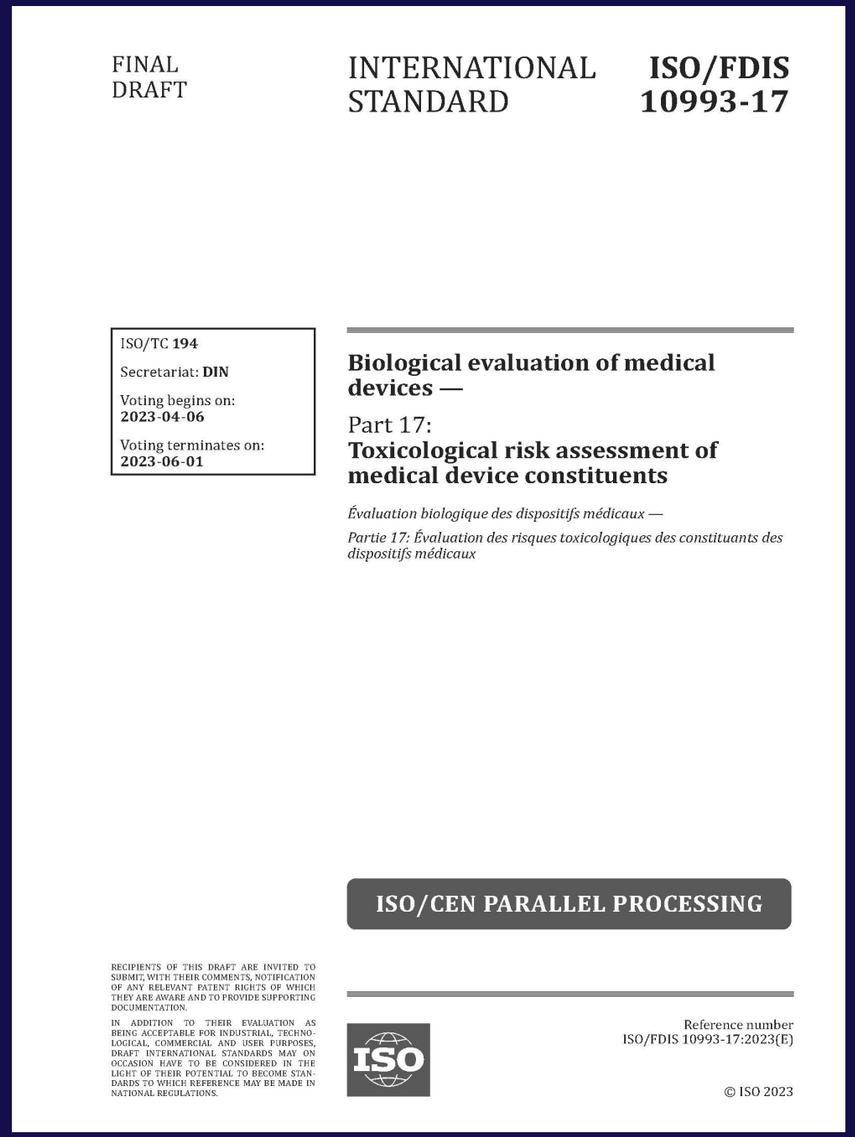
ISO/FDIS 10993-17:2023

Toxicological Risk Assessment of Medical Device Constituents

- Significant update of ISO 10993-17:2002
  - ✓ 11 clauses, 6 annexes, 74 pages
  - ✓ Our for voting & comments (May 7th)
- New concepts
  - ✓ Toxicological risk assessment (TRA)!
  - ✓ Margins of Safety (MOS)
  - ✓ Point of Departure (POD)
  - ✓ Release Kinetics (RK)
  - ✓ Total Quantity (TQ)



FINAL DRAFT

INTERNATIONAL STANDARD

ISO/FDIS 10993-17

ISO/TC **194**

Secretariat: **DIN**

Voting begins on: **2023-04-06**

Voting terminates on: **2023-06-01**

Biological evaluation of medical devices —

Part 17:
Toxicological risk assessment of medical device constituents

Évaluation biologique des dispositifs médicaux —

Partie 17: Évaluation des risques toxicologiques des constituants des dispositifs médicaux

ISO/CEN PARALLEL PROCESSING

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Reference number
ISO/FDIS 10993-17:2023(E)

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ISO/FDIS 10993-17:2023

- Concepts that are going away
  - ✓ Allowable Limit (AL)
  - ✓ Benefit Factor (BF)
  - ✓ Proportional Exposure Factor (PEF)
  - ✓ Utilization Factor (UF)
  - ✓ Tolerable Exposure (TE)

ISO/FDIS 10993-17:2023

New Tools

- Threshold of Toxicological Concern (TTC)
- Toxicological Screening Limit (TSL)
- Estimated Exposure Dose (EED)
- Read-Across (RA)

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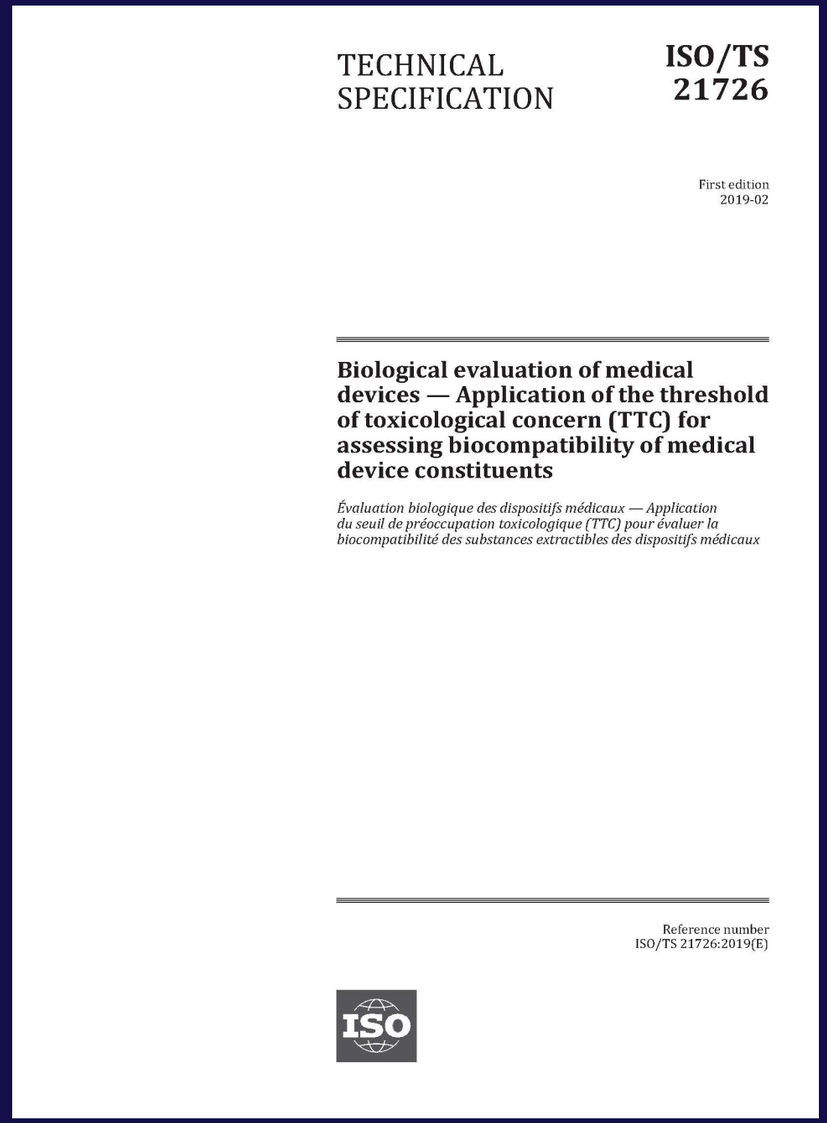
THRESHOLD OF TOXICOLOGICAL CONCERN

"TTC is a pragmatic risk assessment tool based on the principle of establishing a human exposure threshold value for all chemicals, below which there is a very low probability of an appreciable risk to human health" – Robert Kroes, 2004

- Concept first proposed by the food industry. – John Frawley, 1967
- Recognized by medical device industry in 2019 → → →



TECHNICAL SPECIFICATION

ISO/TS 21726

First edition
2019-02

Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

Évaluation biologique des dispositifs médicaux — Application du seuil de préoccupation toxicologique (TTC) pour évaluer la biocompatibilité des substances extractibles des dispositifs médicaux

Reference number
ISO/TS 21726:2019(E)

ISO

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APPLICABILTY OF TTC

- Used for chemicals which lack toxicity data.
- Protective for carcinogens, systemic toxicants, and reproductive/developmental toxicants.
- Not applicable to cytotoxicity, irritation, sensitization, hemocompatibility, or material mediated pyrogenicity.
- Not applicable to Cohort of Concern constituents.

Source: ISO/TC 71726:2019

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RECOMMENDED TTC VALUES

Contact Category	Limited (< 24 h)	Prolonged (24 h to 30 d)	Long-term (> 30 d)		
Duration of body contact	< 1 month		> 1 month to 1 year	> 1 year to 10 years	> 10 years to lifetime
Daily intake (µg/day) of any one constituent	120		20	10	1.5

Recommended ICH M7(R1) TTC values based on ISO 10993-1 medical device contact category

Source: Clause 5.2, ISO/TS 21726:2019

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TOXICOLOGICAL SCREENING LIMIT

- The Toxicological Screening Limit (TSL) can be used to establish whether the Total Quantity (TQ) of a constituent, which is present or extracted, is too low to elicit genotoxicity, cancer, systemic toxicity, or reproductive/developmental toxicological risk.

- When the TQ is below the specified TSL, the quantity can be judged to be of negligible toxicological risk and no further risk evaluation is recommended for these systemic harms.

- Use of TSL is optional.

Source: Clause 6.2.2, ISO/FDIS 10993-17:2023

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APPLICABILTY OF TSLs

TSLs shall not apply to:

- Long-term use in infants or neonates,
- When the nature of harm is irritation,
- Cohort of concern substances,
- Unknown constituents,
- VOCs from gas pathways.

Source: Clause B.1, ISO/FDIS 10993-17:2023

TOXICOLOGICAL SCREENING LIMIT DEFAULT VALUES

Period of assumed exposure to the constituent (d)	**TTC** (µg/d)	**D** (d)	**TSL** (µg)
≤30	120	1	120 (i.e., 120 µg/d × 1 d)
>30	20	30	600 (i.e., 20 µg/d × 30 d)

Source: Clause B.2, ISO/FDIS 10993-17:2023

APPLICATION OF TOXICOLOGICAL SCREENING LIMITS

Medical device contact duration	Period of assumed exposure to the constituent		
	1 d	≤30 d	>30 d
Limited (≤1 d)	TSL ≤30 d = 120 µg	Not applicable	Not applicable
Prolonged (≤30 d)	TSL ≤30 d = 120 µg	TSL ≤30 d = 120 µg	Not applicable
Long-term (>30 d)	TSL≤30 d = 120 µg	TSL ≤30 d = 120 µg	TSL >30 d = 600 µg

If TQ > TSL, then conducting a TRA is necessary.

If TQ < TSL, then the constituent is screened out.

Source: Clause B.3, ISO/FDIS 10993-17:2023

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TSL SUMMARY

- ✓ Protective for genotoxicity, cancer, systemic toxicity, reproductive, or developmental toxicity.
- ✓ May significantly reduce the number of chemicals for the toxicological risk assessment.
- ✓ Optional, but helpful.
- ✓ Saves time and effort.

Source: Annex B, ISO/FDIS 10993-17:2023

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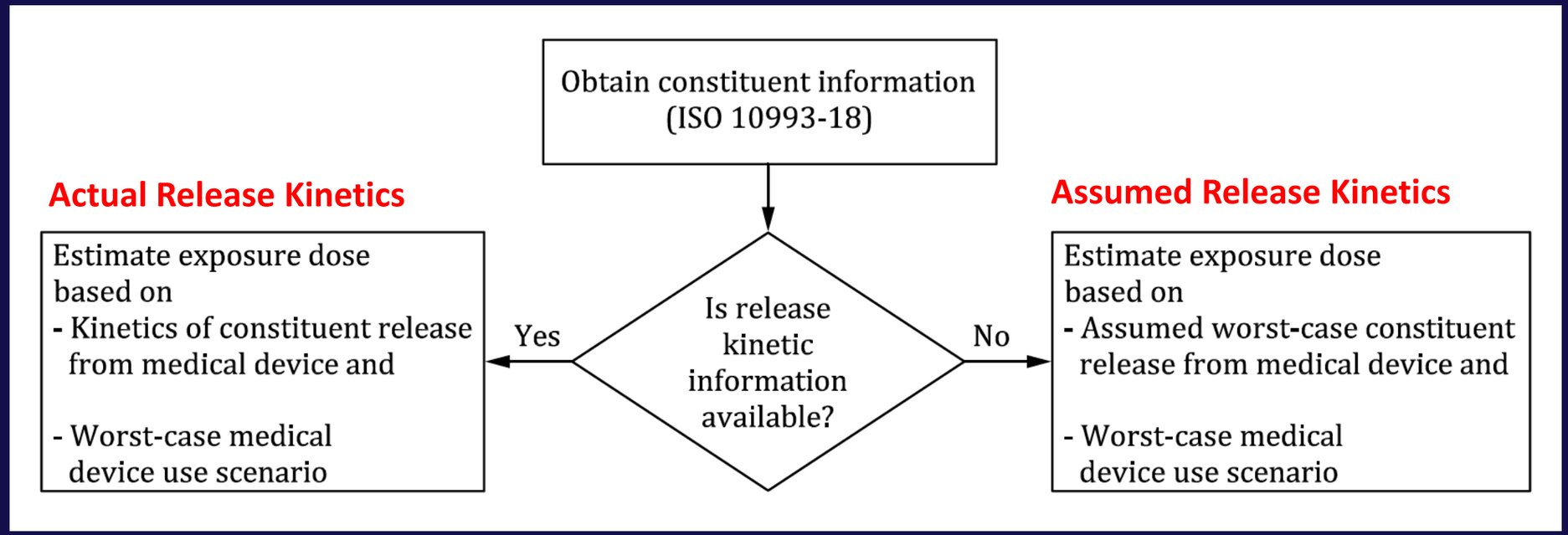
ESTIMATED EXPOSURE DOSE

"A worst-case estimated exposure dose (EED_{max}) for each reportable constitute shall be estimated"



Source: Clause 8, Annex E, ISO/FDIS 10993-17:2023

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ASSUMED RELEASE KINETICS

For prolonged or long-term contact medical devices without release kinetics data, the exposure dose can be calculated with this equation:

$$EED_{max} = (TQ \times SF_{a.r.}) / BW_L / R_d$$

Where:

EED_{max} Worst-case exposure of a constituent;

TQ Total quantity, in µg, extracted from the medical device;

$SF_{a.r.}$ Scaling factor applied when the assumed release (a.r.) is used;

BW_L Lowest body weight, in kg, of the patient;

R_d Assumed release duration, in d, (i.e., lowest number of exposure days).

Source: E.3, ISO/FDIS 10993-17:2023

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ASSUMED RELEASE KINETICS

Assumed (i.e., default) release durations (Rd) shall be applied based on the shortest duration of constituent exposure of each period of assumed exposure as presented this table.

Medical device contact duration category	R_d for each time period of assumed constituent exposure (d)			
	≤1 d	2 d to 30 d	31 d to 365 d	≥366 d
Prolonged (≤30 d)	1	2	Not applicable	Not applicable
Long-term (31 d to 365 d)	1	2	31	Not applicable
Long-term (≥366 d)	1	2	31	366

Source: E.3, ISO/FDIS 10993-17:2023

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MOS CALCULATION

- Select a constituent's TI/TTC or TCL for an appropriate exposure duration.
- Use it with the corresponding EED_{max} to calculate the MOS:

$$MOS = \frac{TI/TTC \text{ or } TCL}{EEDmax}$$

Source: Clause 9, ISO/FDIS 10993-17:2023

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TOXICOLOGICAL RISK ACCEPTANCE CRITERIA

- An exposure dose of a constituent is without appreciable harm to health when the following apply:
  - ✓ MOS exceeds 1
  - ✓ Contributing values to the MOS are conservative

- Toxicological risk shall be further addressed by other means in accordance with ISO 10993-1 and ISO 14971 when any of the following apply:
  - ✓ MOS is below 1 based on release kinetics and TI or TCL are used,
  - ✓ Cancer risk of a human carcinogen exceeds 1 in 100 000, or
  - ✓ The MOS is judged to represent possible toxicological risk.

Source: Clause 10, ISO/FDIS 10993-17:2023

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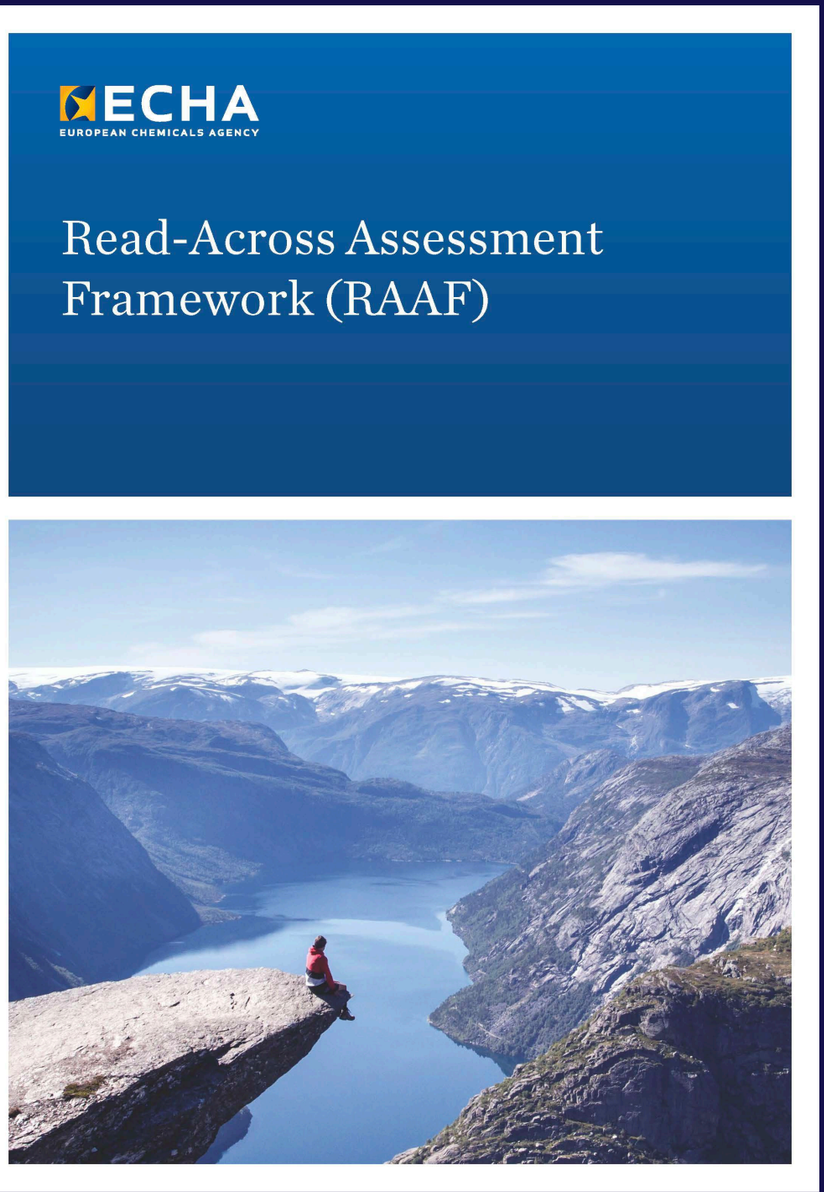
READ-ACROSS

- A data-gap filling process for data-poor chemicals.
- Analog approach: One-to-one structural matching.
- Category approach: Chemical similarity grouping.
- Goal: Chemical and toxicological similarity.
- Tools: AIMBIT, GenRA, QSAR Toolbox, ToxMatch.

Source: Patelewicz et al., 2017



European Chemicals Agency, 2017

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NEW TOOLS SUMMARY

- ✓ The new ISO/FDIS 10993-17 tools are optional,
- ✓ but they have the potential to save time and effort,
- ✓ and help produce more focused and accurate TRAs.

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UPDATE ON IN VITRO IRRITATION TESTING

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TIMELINE

2009 – ISO/TC 194 Meeting in Berlin

2010 – Research Begins at Medtronic

2012 – Pilot Project Completed

2017 – Round Robin Study Completed

2019 – Follow-Up Study Completed

2021 – ISO 10993-23 Published by ISO (January)

2021 – EN ISO 10993-23 Published by CEN (March)

2021 – EN ISO 10993-23 Published in OJEU (July)

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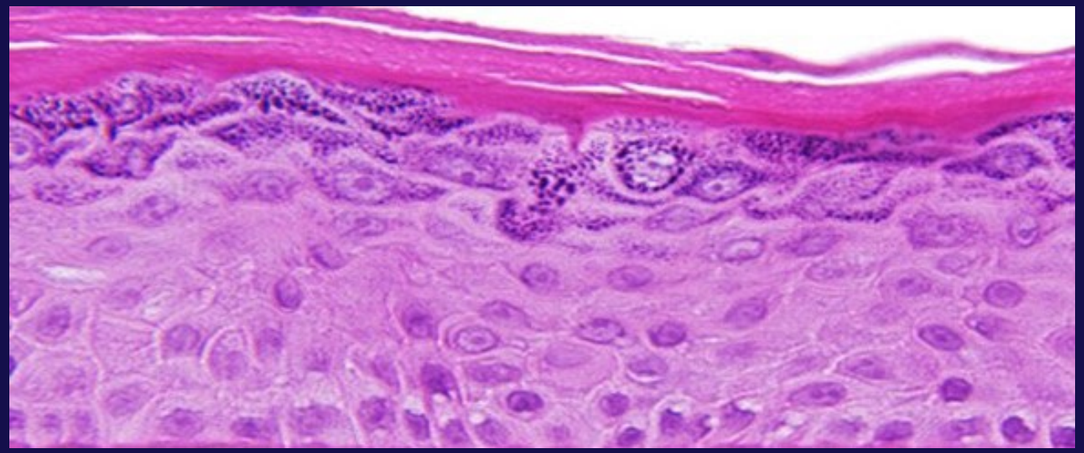
ROUND ROBIN STUDY (2013-2018)

- 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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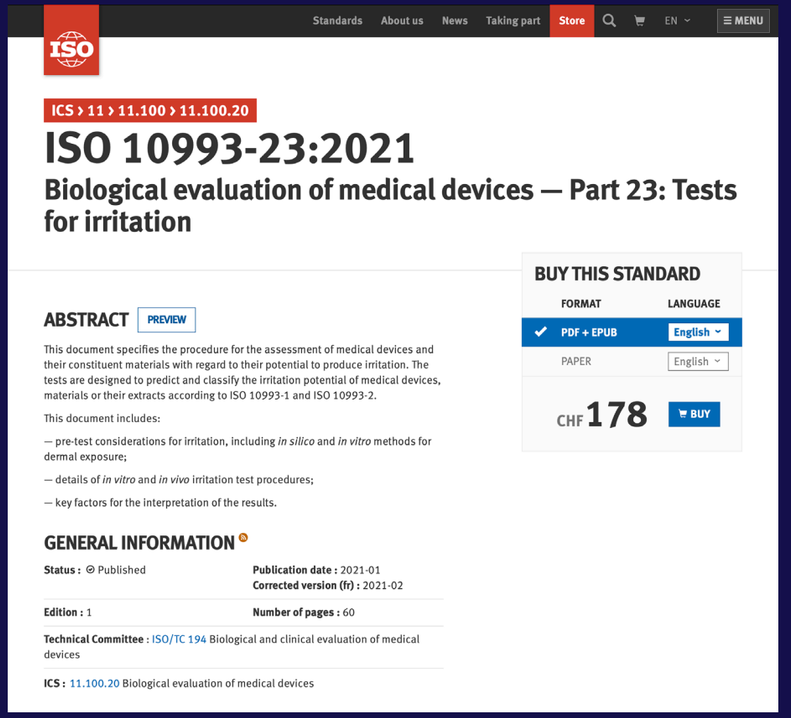
KEY CHANGES IN ISO 10993-23:2021

- Clause 1. Scope now includes in vitro testing
- Clause 4. General principles statement:
  "Therefore, the in vitro irritation test shall be performed before animal testing or human patch test is considered."
- Clause 6. In vitro irritation tests – 11 pages of materials & methods
- Annex B. Test method check list for in vitro testing
- Annex C. Documentation sheet for RhE tissue testing



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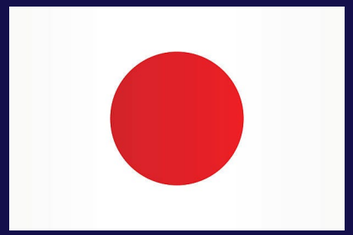
COST AND TURNAROUND TIME

- Pricing varies by tissue brand and geographic location.
- CROs are currently charging from $3100 – $7800.
- Some offer discounts when running two devices at once.
- Turnaround times (TAT) range from 30 to 90 days.
- As labs gain more experience, prices and TAT may drop.

REGULATORY RECOGNITION

Asia	Europe	CEN & EU	CEN & EU	CEN & EU	CEN & EU	CEN & EU	CEN Affiliates
China	Austria	Denmark	Hungary	Luxembourg	N. Macedonia	Sweden	Albania
Japan	Belgium	Estonia	Iceland	Malta	Romania	Switzerland	Bosnia and
	Bulgaria	Finland	Ireland	Netherlands	Serbia	Turkey	Herzegovina
	Croatia	France	Italy	Norway	Slovakia	U.K.	Montenegro
	Cyprus	Germany	Latvia	Poland	Slovenia		
	Czech Rep.	Greece	Lithuania	Portugal	Spain		



39 Countries in Asia & Europe

Nearly 2 billion people

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PENDING RECOGNITION OF ISO 10993-23

- Some key countries have not yet recognized Part 23
  - ✓ Australia
  - ✓ Canada
  - ✓ Republic of Korea
  - ✓ United States
- This has led to Dual Testing (i.e., in vitro & in vivo)
- ISO/TC 194 WG 8 is working to address this situation

REFERENCES

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REFERENCES

De Jong WH, et al. 2018. Round robin study to evaluate the reconstructed human epidermis (RhE) model as an in vitro skin irritation test for detection of irritant activity in medical device extracts. *Toxicology In Vitro* 50:439-449. **Open Access**

De Jong WH, Carraway JW, Liu C, Fan C, Liu J, Turley AP, Rollins TS, Coleman KP. 2020. The suitability of reconstructed human epidermis models for medical device irritation assessment: A comparison of In Vitro and In Vivo testing results. *Toxicology In Vitro.* 69:104995. **Open Access**

Patlewicz, G., et al. 2017. Navigating through *the minefield of read-across tools: A review of in silico tools for grouping. Computational Toxicology* 3:1–18. **Open Access**

Pellevoisin, C., Coleman, KP., and Hoffmann, S. 2022. ISO 10993-23 In vitro irritation testing for medical devices: Substantiating applicability to mild irritants and non-extractables. *Toxicology in Vitro* 82:105371.

THANK YOU

Split Rock Lighthouse, Lake Superior
Minnesota Historical Society

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