Research at CDRH to Evaluate Medical Device Safety Using Alternative Approaches

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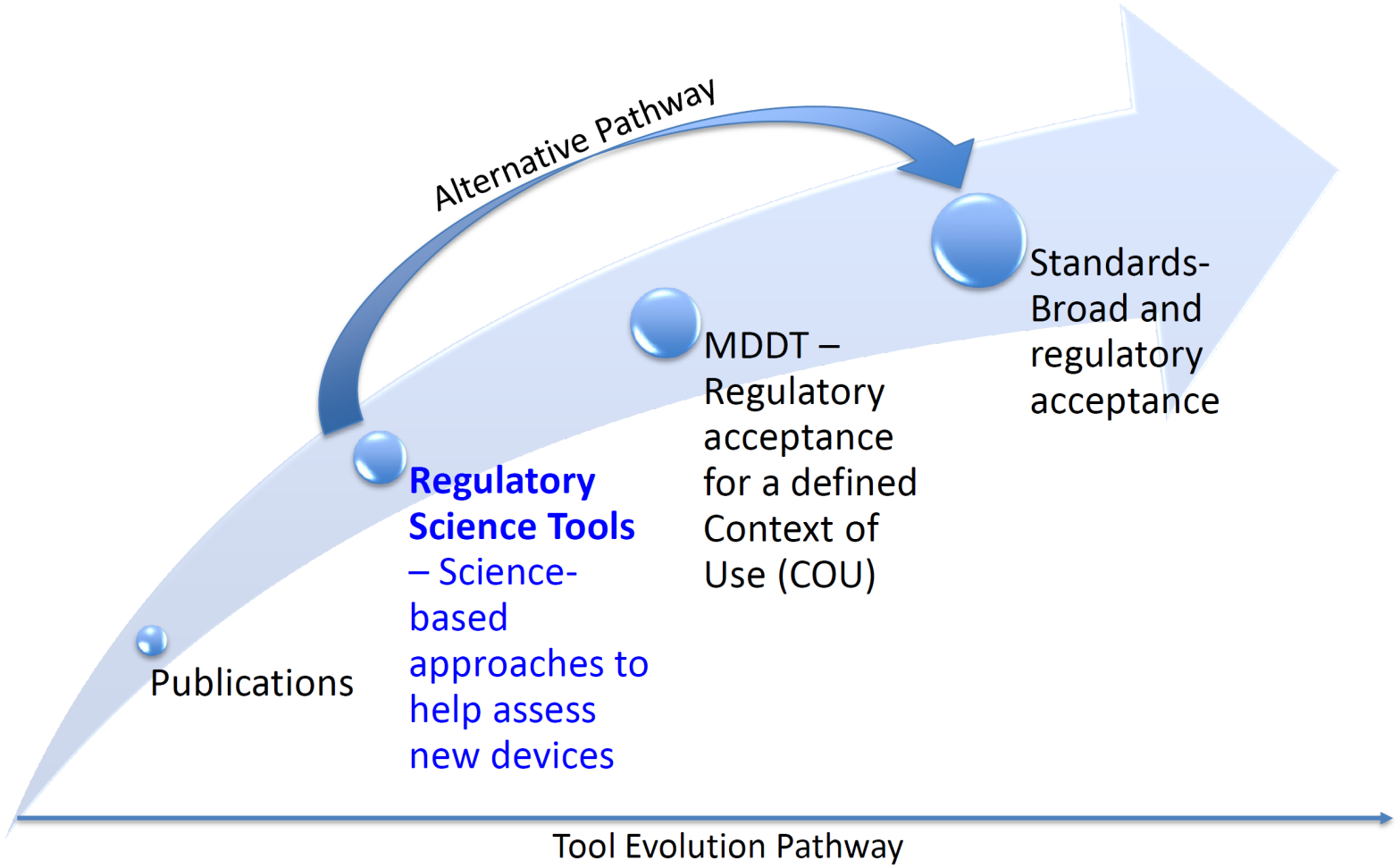
*CDRH's Office of Science and Engineering Laboratories (OSEL) aims to **accelerate** patient access to innovative, **safe** and effective medical devices through best-in-the-world regulatory science.*

Regulatory Science Tools (RSTs)

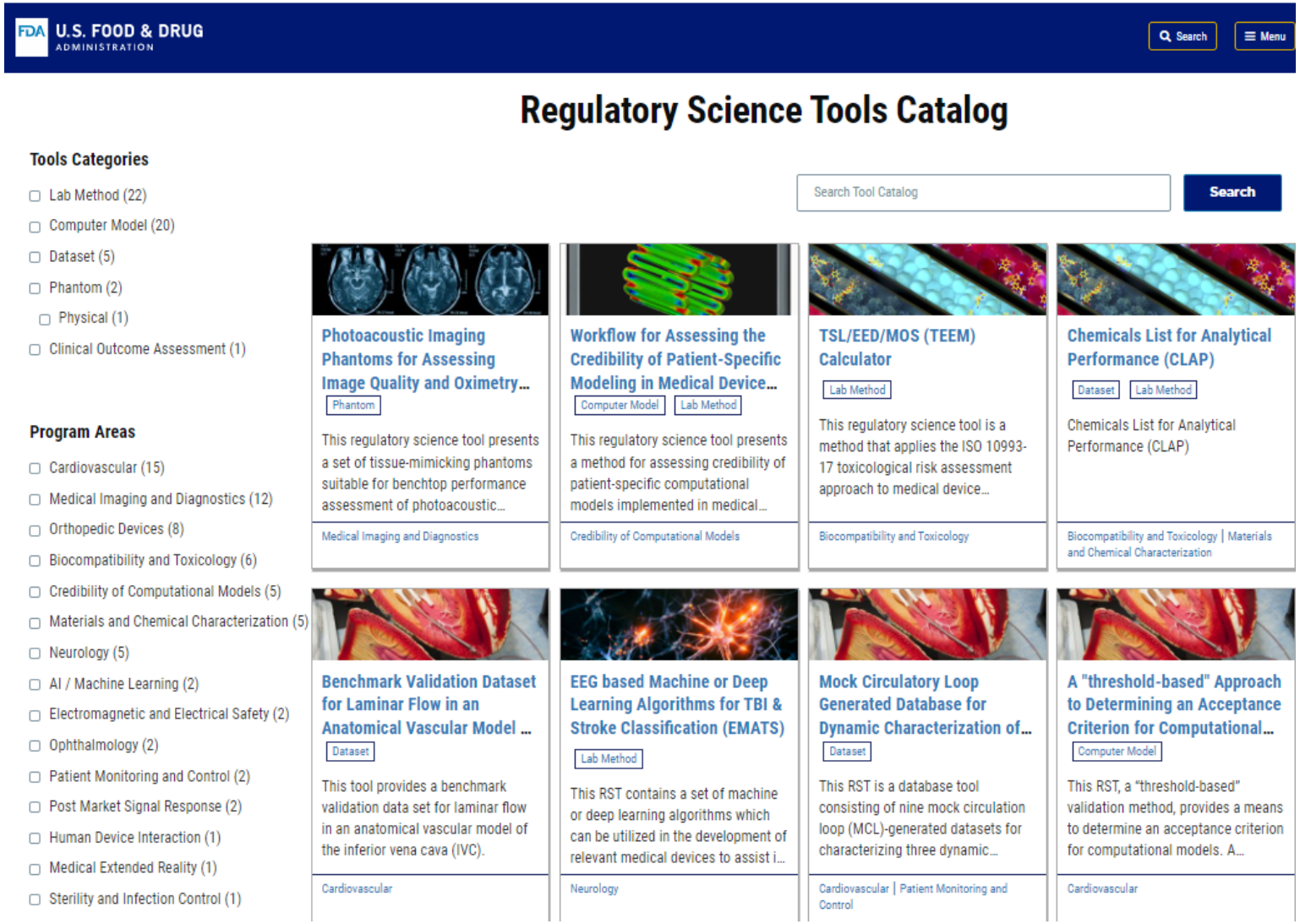
RSTs are peer-reviewed tools where standards & qualified MDDTs don't exist.

Stakeholder feedback plays a key role in determining what RSTs we develop.



MDDT = Medical device development tool

Regulatory Science Tool Catalog



https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices

How Is Medical Device Biocompatibility Addressed Today?

C = may be addressed through chemical characterization. ✓, in vitro test. ●, typically addressed through animal testing.

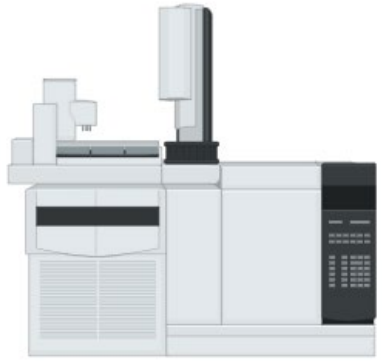
Category	Contact	Contact duration A = Limited (< 24 hr) B= Prolonged (24 hr – 30d) C = Long term (> 30d)	Cytotoxicity	Sensitization	Irritation	Acute Toxicity	Pyrogenicity	Subacute/ Subchronic Tox.	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity
Surface device	Intact skin	A, B, C	✓	●	●								
	Mucosal membrane	A	✓	●	●								
		B	✓	●	●	C	●	C		●			
		C	✓	●	●	C	●	C	✓C	●		C	
	Breached or compromised surface	A	✓	●	●	C	●						
		B	✓	●	●	C	●	C		●			
		C	✓	●	●	C	●	C	✓C	●		C	C
External communicating device	Blood path, indirect	A	✓	●	●	C	●						
		B	✓	●	●	C	●	C			✓●		
		C	✓	●	●	C	●	C	✓C	●	✓●	C	C
	Tissue/bone dentin	A	✓	●	●	C	●						
		B	✓	●	●	C	●	C	✓C	●			
		C	✓	●	●	C	●	C	✓C	●		C	C
	Circulating blood	A	✓	●	●	C	●		✓C				
		B	✓	●	●	C	●	C	✓C	●	✓●		
		C	✓	●	●	C	●	C	✓C	●	✓●	C	C
Implant	Tissue/bone	A	✓	●	●	C	●						
		B	✓	●	●	C	●	C	✓C	●			
		C	✓	●	●	C	●	C	✓C	●		C	C
	Blood	A	✓	●	●	C	●		✓C	●	✓●		
		B	✓	●	●	C	●	C	✓C	●	✓●		
		C	✓	●	●	C	●	C	✓C	●	✓●	C	C

Adapted from FDA's 2023 Guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Alternatives Under Investigation

1. How can Weight of Evidence (WoE) be better leveraged to evaluate medical device safety?
   - WoE approach for risk of changing from ethylene oxide to vaporized hydrogen peroxide sterilization
   - Evaluation of published WoE frameworks
   - Can we identify “safe harbor” materials?

2. How can chemistry information from the device be used to evaluate local toxicity endpoints that currently use animal testing?
   - Irritation
   - Sensitization



Can Weight of Evidence Be Used to Evaluate Medical Device Safety?

VHP Risk Assessment Tool

Why is it needed?

- Upcoming EPA regulations are expected to lead many medical device manufacturers to change from ethylene oxide (EtO) to vaporized hydrogen peroxide (VHP) that will lead to biocompatibility testing to support these changes
- ~50% of sterilized devices are currently sterilized with EtO

What is it?

- A framework for manufacturers and reviewers to ensure consistent evaluation of legacy devices to assure reasonable safety when changing sterilization modalities from EtO to VHP.

What does it provide?

- A framework for a stepwise evaluation and testing process to address performance and safety risks for durable polymers and metals.

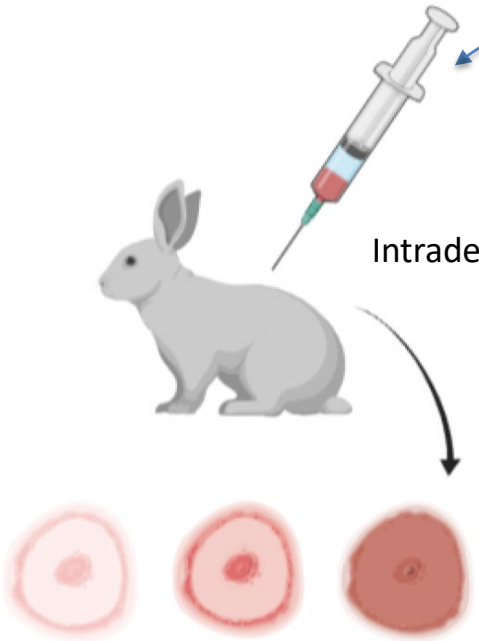
Multiple Lines of Evidence Considered to Evaluate Safety and Performance for Change from EtO to VHP

Lines of Evidence to Consider
DEFINED SCOPE: • Device is legally marketed in the US with an acceptable clinical history. • Only change is ethylene oxide (EtO) to vaporized hydrogen peroxide (VHP) on durable polymers and metals.
MATERIAL CHARACTERIZATION: VHP's effects on degradation, visual, surface, and performance in comparison to EtO-sterilized materials.
CHEMICAL CHARACTERIZATION: Analytical chemistry testing and demonstrated chemical equivalence or justification as to why testing is not necessary (e.g., materials and likely constituents aren't likely to be oxidized or have demonstrated safety in an oxidative environment).
BIOCOMPATIBILITY/TOXICOLOGY: • Residual H_2O_2 is appropriately controlled. • Risk assessment of chemistry changes, if needed.

Can chemistry information on a device be used to evaluate local endpoints (e.g., irritation, sensitization)?

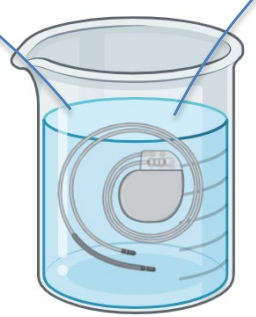
How Are Sensitization & Irritation Potential Of Medical Devices Evaluated Today?

Irritation: Intracutaneous Reactivity/Irritation
ISO 10993 - 23



Intradermal injection

Scoring



Medical device extract
per ISO 10993-12

Sensitization: Guinea Pig Maximization Test
ISO 10993-10

Intradermal induction w/ adjuvant

Epidermal induction

Rest period with no treatment

Epidermal challenge & scoring

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How Do Other Sectors Evaluate Local Toxicity Endpoints?

Irritation

- In vitro testing
- Human testing
- Hazard assessment
- Threshold limits (e.g., PQRI*)

Sensitization

- In vitro / in chemico testing
- Human repeat patch testing
- Quantitative risk assessment (QRA)
- In silico prediction models
- Defined approaches
- Threshold limits (e.g., PQRI*)

PQRI: Product Quality Research Institute

Can Chemistry Be Used to Address Irritation & Sensitization for Medical Devices?

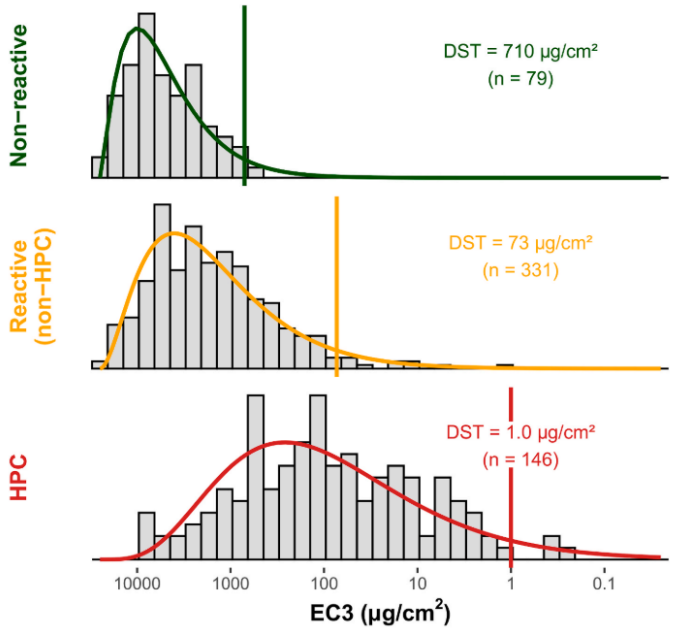
Is the chemistry testing conducted on medical device extracts sensitive enough?

- Analytical evaluation threshold (AET) is based on systemic toxicity (ISO 10993-18)

How can chemistry be used to evaluate skin irritation and sensitization risk?

- Threshold value?
- Hazard assessment?
- Quantitative risk assessment?
- Considering weight of evidence?
- Tiered approach?

Dermal Sensitization Threshold For Dermal Exposure



Chilton, et al. (2022). Updating the Dermal Sensitisation Thresholds using an expanded dataset and an in silico expert system. *Regulatory Toxicology and Pharmacology, 133, 105200.*

How Can You Contribute?

1. Stakeholder feedback drives our regulatory science research

2. Collaboration increases capacity and helps to develop these alternative methods more quickly

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Catalog of Regulatory Science Tools to Help Assess New Medical Devices

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