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International Standards as the Bridge to the Future of Safe Medical Devices

ESTIV Congress 2026
30 June 2026

Co-chairs:

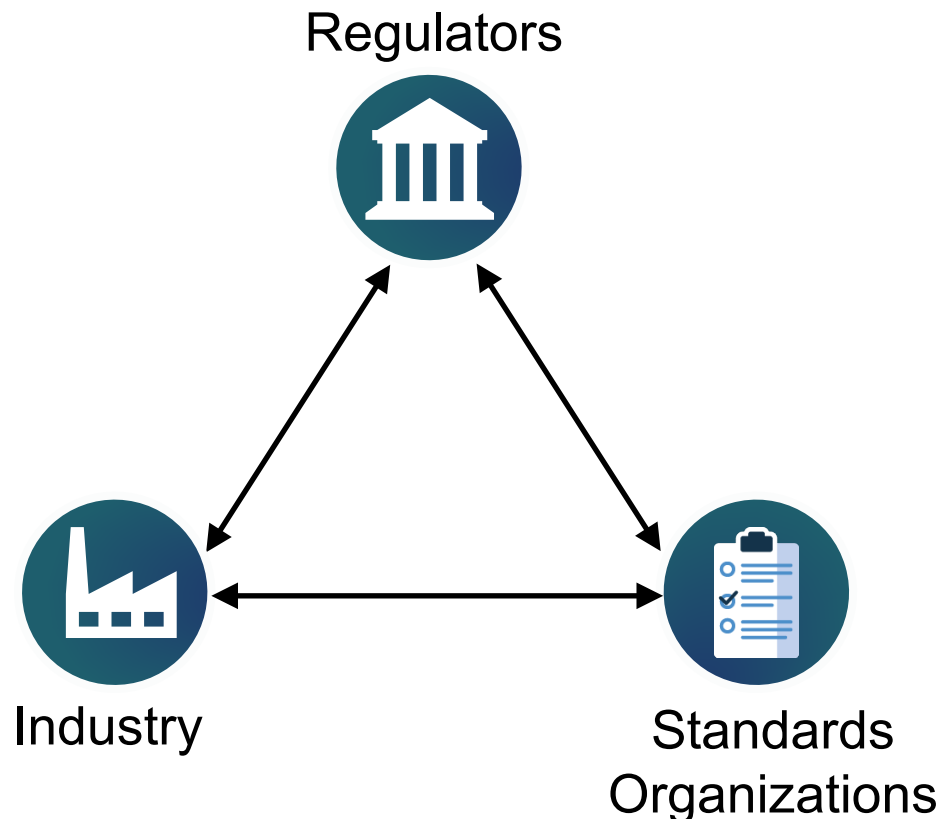
Helena Kandarova (Institute of Experimental Pharmacology and Toxicology)

Jessica Perrin (PETA Science Consortium International e.V.)

PETA SCIENCE CONSORTIUM
INTERNATIONAL e.V. 

Global adoption of NAMs for medical devices

The “awkward triangle”



Janine Townsend
(Chorley Consulting)

Seyoum Ayehunie
(MatTek, Now Part of Sartorius)

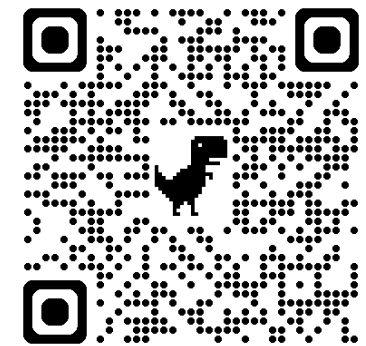
Kelly Coleman
(Medtronic)

Shabnam Solati
(MAT BioTech)

Lindsey Borton
(Gradient)

Amanda Ulrey
(Institute for In Vitro Sciences)

**Presentations
Literature & Resources**



www.thepsci.eu/estiv2026



Janine Townsend

Janine.townsend@chorleyconsulting.co.uk



Director at Chorley Consulting, an independent toxicology company supporting manufacturers with the biological safety of their medical devices



MSc. Global aquatic conservation and management
BSc. Molecular biology and biotechnology



10 years experience in biological evaluation of medical devices and a further 10 years in regulatory roles across the cosmetics, general products and fragrance industries (RB & Symrise)

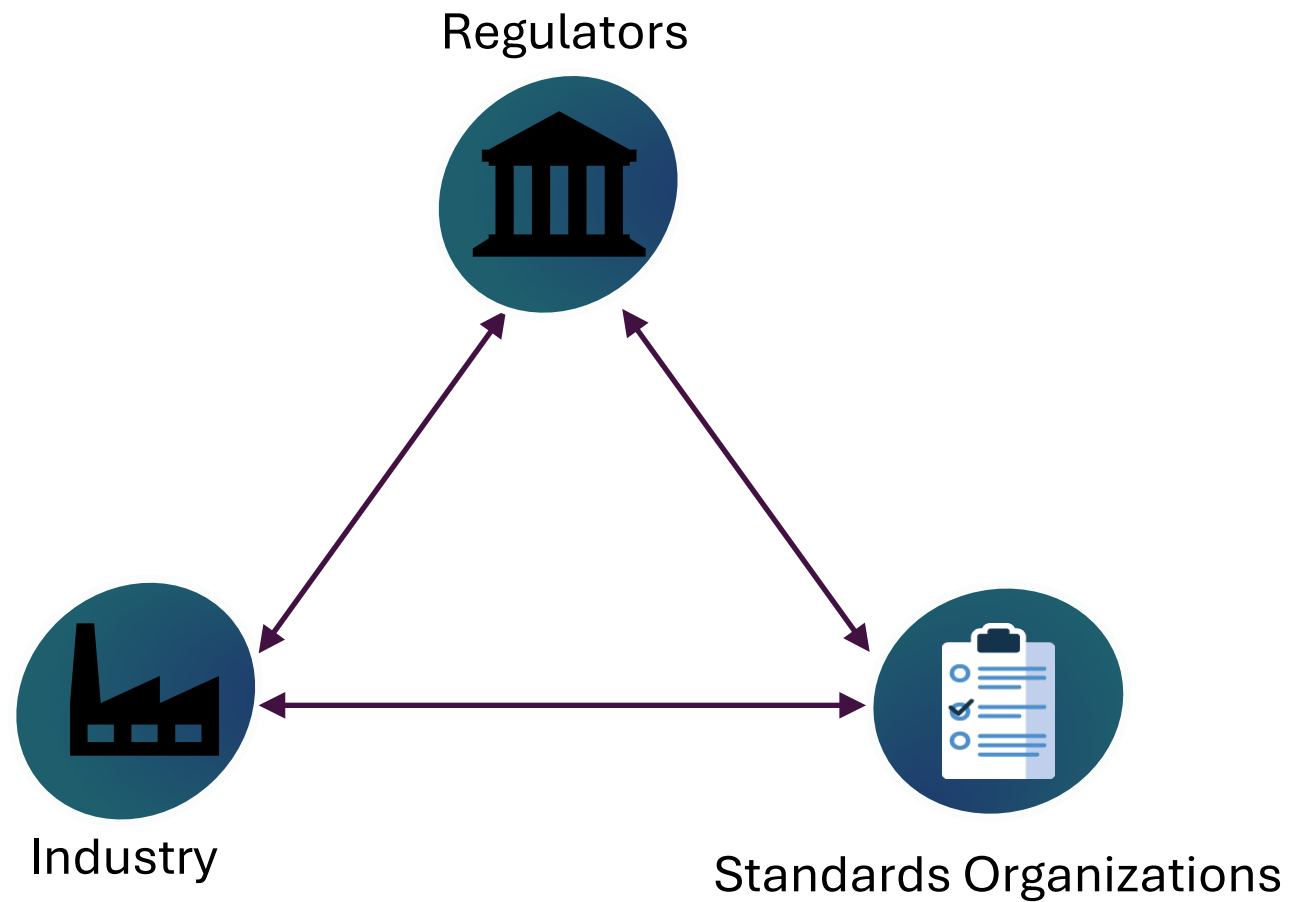
Member of: BSI TC/194, ISO 10993 WG's 1, 3 & 15 & ESTIV

PRACTICAL CHALLENGES TO THE USE OF NAMS FOR MEDICAL DEVICES – WHEN STATE-OF-THE-ART SCIENCE ALONE IS NOT ENOUGH

Janine Townsend

ESTIV, June 2026

THE “AWKWARD TRIANGLE”



BIOLOGICAL SAFETY OF MEDICAL DEVICES

Guidance on how to conduct a biological evaluation of a Med Device

Based on contact type and duration

Defines biological effects to consideras well as a multitude of other things

Common biological effects across all medical devices are:

- Cytotoxicity
- Irritation
- Sensitisation

“ISO 10993 series is intended for use by professionals, appropriately qualified by training and experience....”



WHAT DO OUR STANDARDS SAY?

ISO 10993-2



4.5 “Testing strategies shall, as appropriate, adopt a tiered or hierarchical approach to minimize both the amount of animal testing required...”

“Animal tests shall not be performed if the available data (e.g. from literature and/or database searches, results from previous screening tests, validated *in vitro* tests, previous animal tests or any other available relevant evidence) provide sufficient information on the biocompatibility of the test material for a sound, relevant risk assessment to be undertaken.”

NOTE

NOTE: Some OECD Methods are listed & accepted in the ISO 10993 Series

4.5 Test strategy — Sequence of *in vitro* and *in vivo* tests
“The rationale for the testing strategy shall be documented”

ISO 10993 ACCEPTED METHODS FOR FINAL MD



Biological endpoint/effect	<i>In vivo</i>	<i>In vitro</i> / <i>In silico</i>	Risk assessment
Cytotoxicity		X	X*
Irritation/Intracutaneous reactivity	X	X*	X*
Sensitisation	X		X*

“State Of The Art?”

10993:23
(2021)

*Not all MD. Based on contact type and/or quality of available data

NOT globally harmonised!

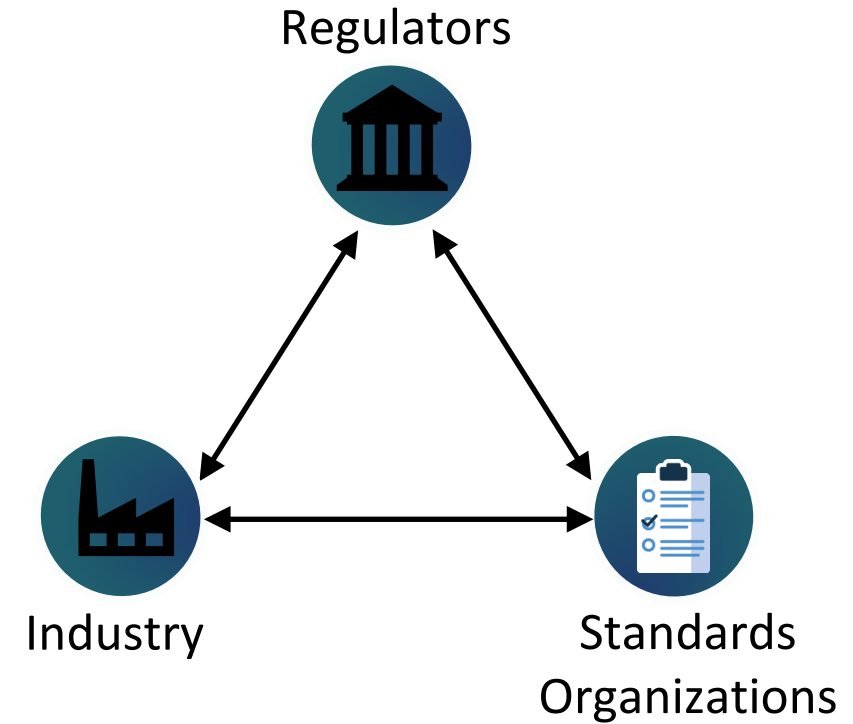
REGULATORS (EU)

Regulators: Notified Bodies

No requirement to have a toxicologist
(experienced/inexperienced) in the review
team

No over-arching EU Body to support disputes
between Manufacturer and NB

= Nervous manufacturers



WHAT ARE THE STANDARDS AND REGULATIONS SAYING?



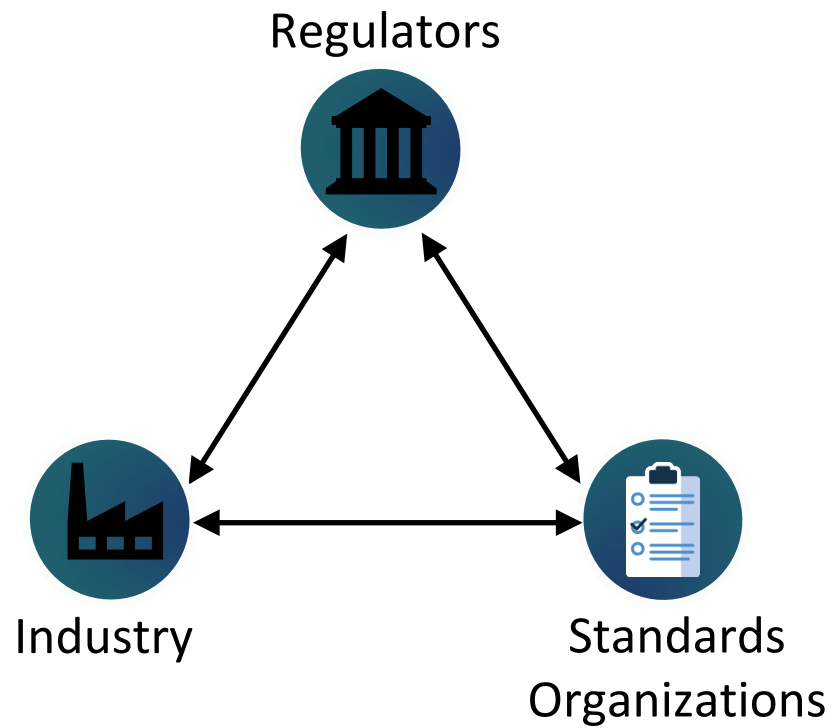
EU Source	NAMS?	State of the art?	3R's?	ISO 10993	Medical device specific?
Directive 2010/63/EU	X		X		
MDR 2017/745		X			X
ISO 10993	X		X	-	X
ISO 13485					X
ISO 14971				X	X

Mandatory/legally enforceable

Best practice/ Advisory
(Not legal) with multiple options and interpretations

ISO 10993 is NOT a
Regulation/Law

INDUSTRY



INDUSTRY

Large, multi-nationals

FMCG

Small-medium with 4-5 devices

Start-ups, University spin outs



This is for the US market, so we had to perform *in vivo* studies



The validated studies are not appropriate for the contact type

We could not find a capable laboratory

Our timelines were too short to fit in the *in vitro* testing

It was cheaper to perform *in vivo* testing



Testing was done prior to the availability of the alternative studies

We did not know it was an option/ We did not know that we were expected to

PRACTICAL CHALLENGES FACED BY MANUFACTURERS

Lack of knowledge

Cost

Timing/Planning

Lack of relevant expertise

Lengthy lab approval process



No legal requirement

No NB support

No financial or time benefit

Not globally accepted

No consequence

WHO IS RESPONSIBLE?

Who is responsible for implementing & policing the 3Rs principle?



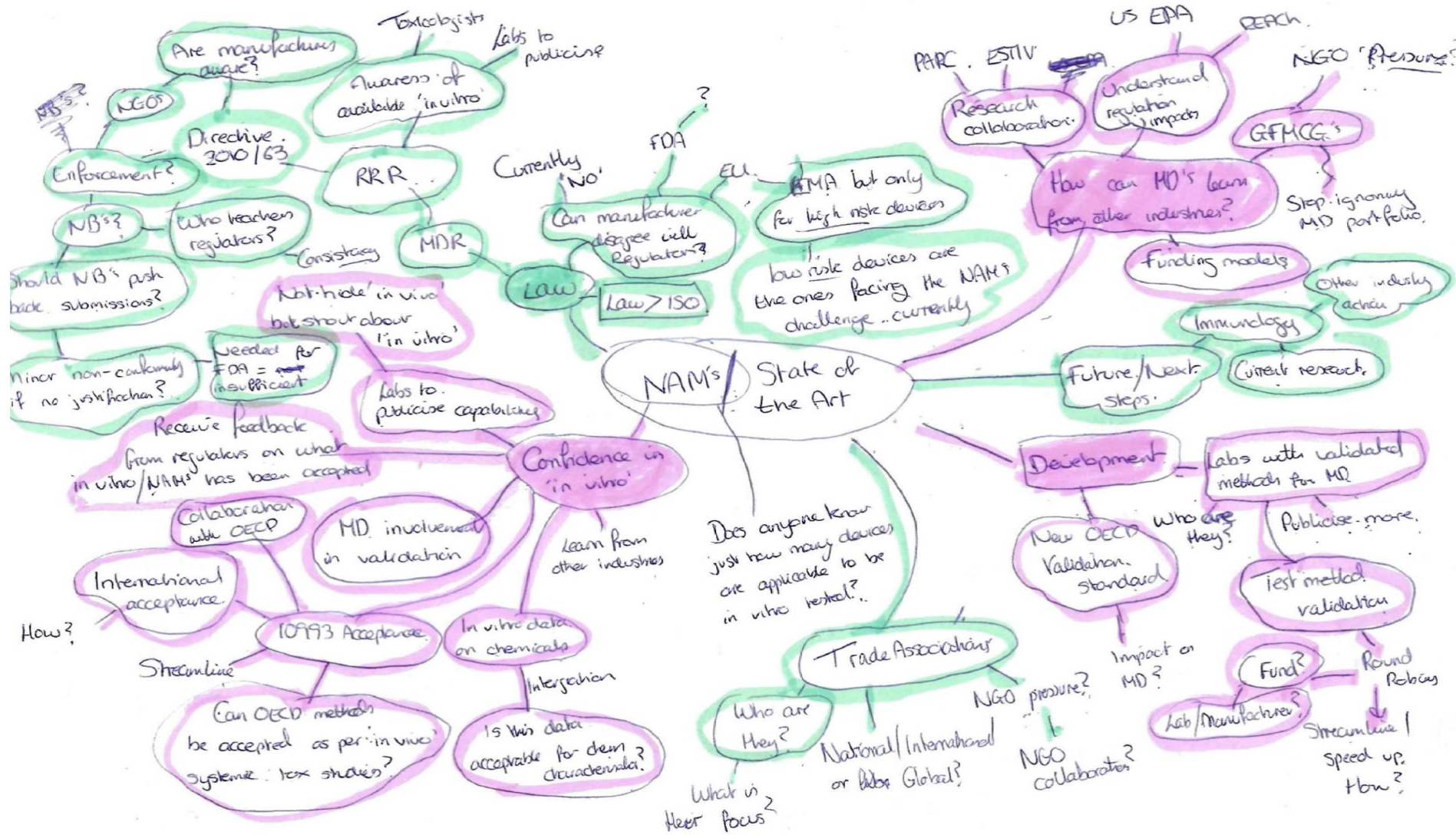
Questionnaire sent to 23 medical device test labs

4/6 Labs have a registered toxicologist

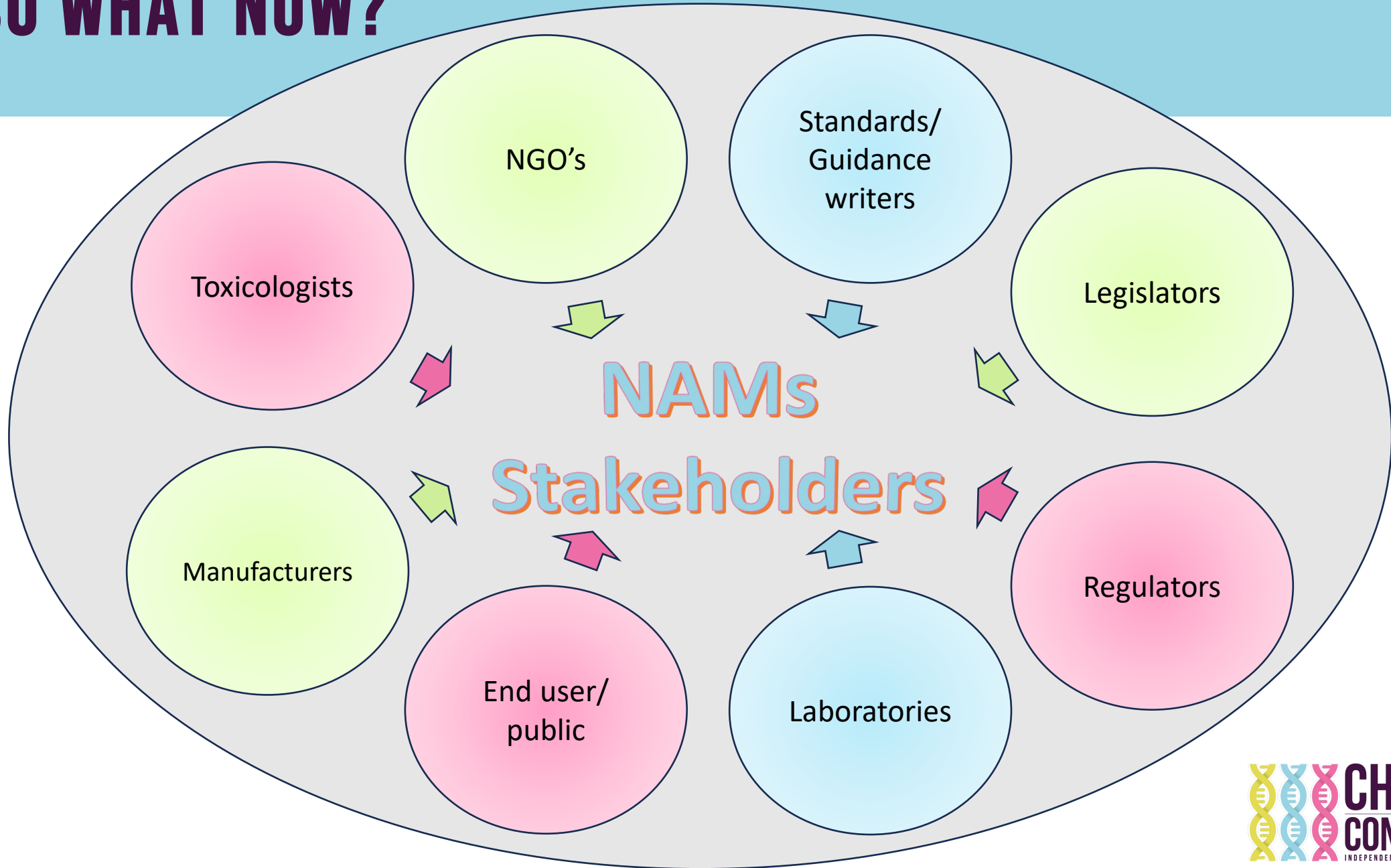
3/6 Labs have a regulatory expert

3/6 Labs confirmed that they review the BEP

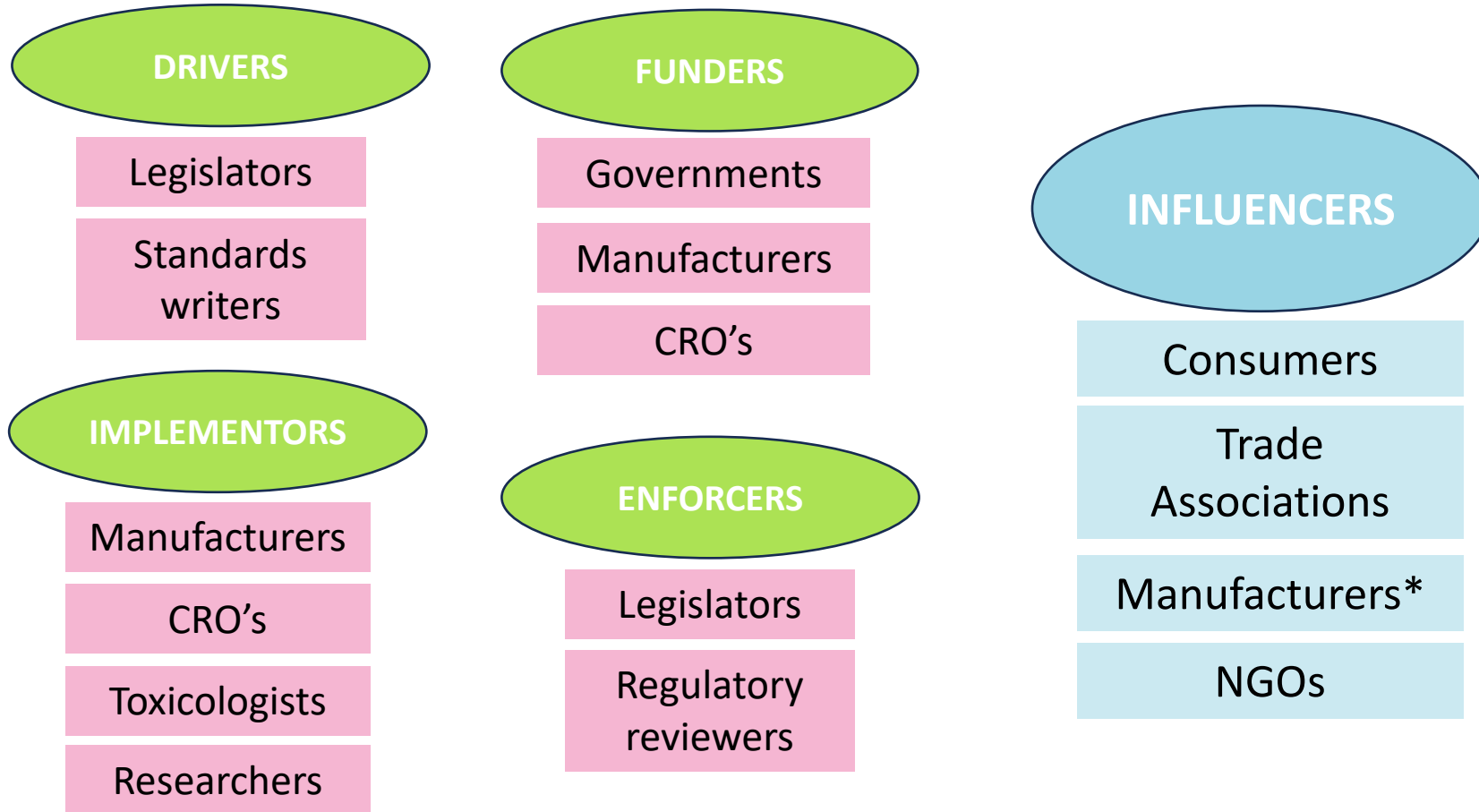
WHY ARE NAMS POSING SO DIFFICULT TO IMPLEMENT FOR MEDICAL DEVICES?



SO WHAT NOW?



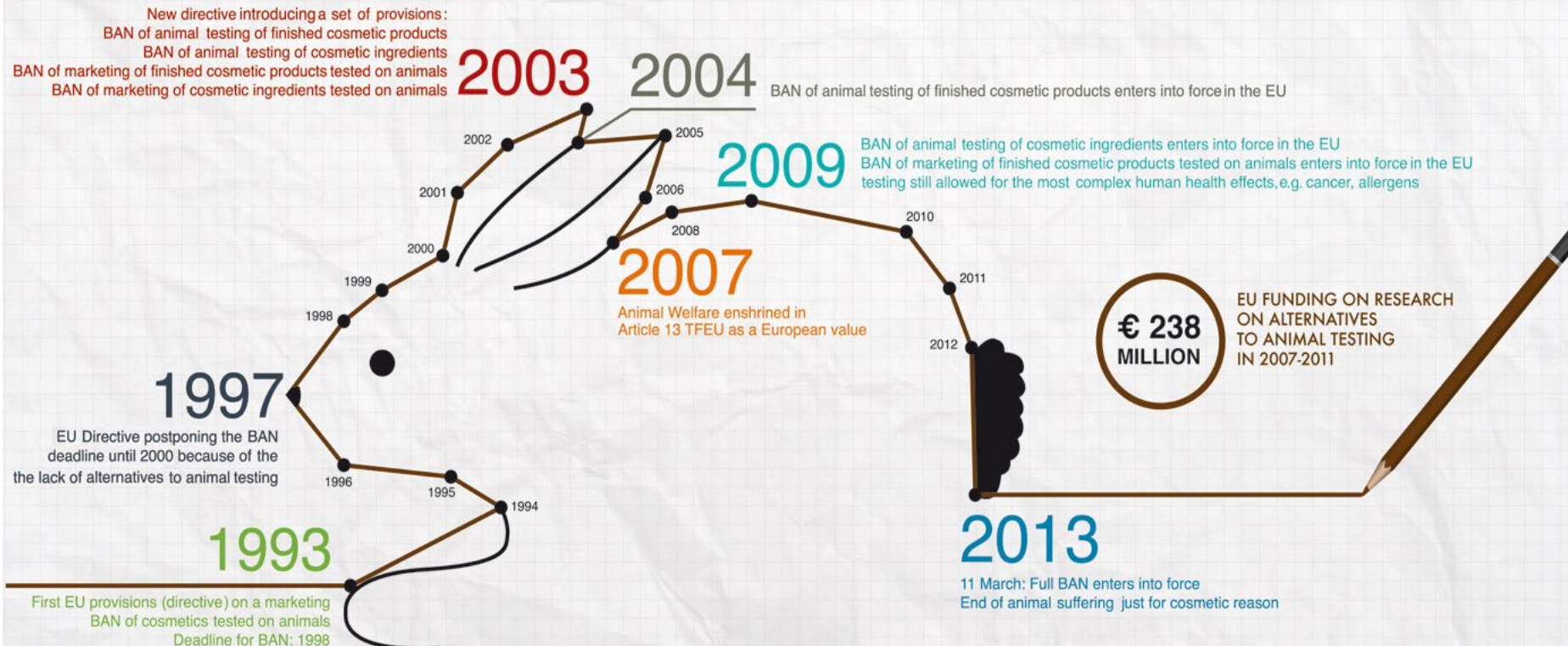
STAKEHOLDER ROLES



*Forward thinking/ ethically mindful manufacturers

IF COSMETICS CAN THEN WHY CAN'T MD'S?

CONNECTING THE DOTS FOR ANIMALS: HISTORY OF THE EU BAN ON ANIMAL TESTING FOR COSMETICS



Trade Associations and consumers pressure the industry/Gov



Regulation is updated



Manufacturers and Government support research and labs to establish more validated studies specific for MD



Increased patient safety and reduction in animals used for testing

COLLABORATION ACROSS INDUSTRIES

Lots of collaborative work and NAMS focused activity in Europe working towards the 3Rs principle is ongoing:



No focus on Medical devices, even though some FMCG members market them



Reviewing the relevance of animal tests listed in the pharmacopeia



European Society of Toxicology In Vitro



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



CONCLUSION

- 1) Stay focused on improving patient safety (not replacing animal studies)
- 2) Raise awareness & confidence of the available State of the Art NAMs for MDs
- 3) Educate and challenge the Regulators and the Manufacturers
- 4) Make the tiered approach and rationale to testing (as per ISO 10993) a non-negotiable LEGAL requirement

CONCLUSION

Cross-Industry collaboration

REMEMBER Med devices are not special..... We can learn from **and with** other industries



THANK YOU FOR LISTENING



DR. SEYOUM AYEHUNIE



Developer of the EpiVaginal tissue model to assess the toxicity of feminine care products, drug responses, and viral infections.



PhD in Virology from the Karolinska Institute, Sweden, Post-Doc at Harvard University Boston, USA in cellular immunology and vaccine development.



28 years of experience working in Biotech to develop human primary cell-based 3D tissue engineering and assay methods to evaluate safety and efficacy of feminine care products, pharmaceutical drugs, disease modelling, and validation of assays for regulatory purposes.



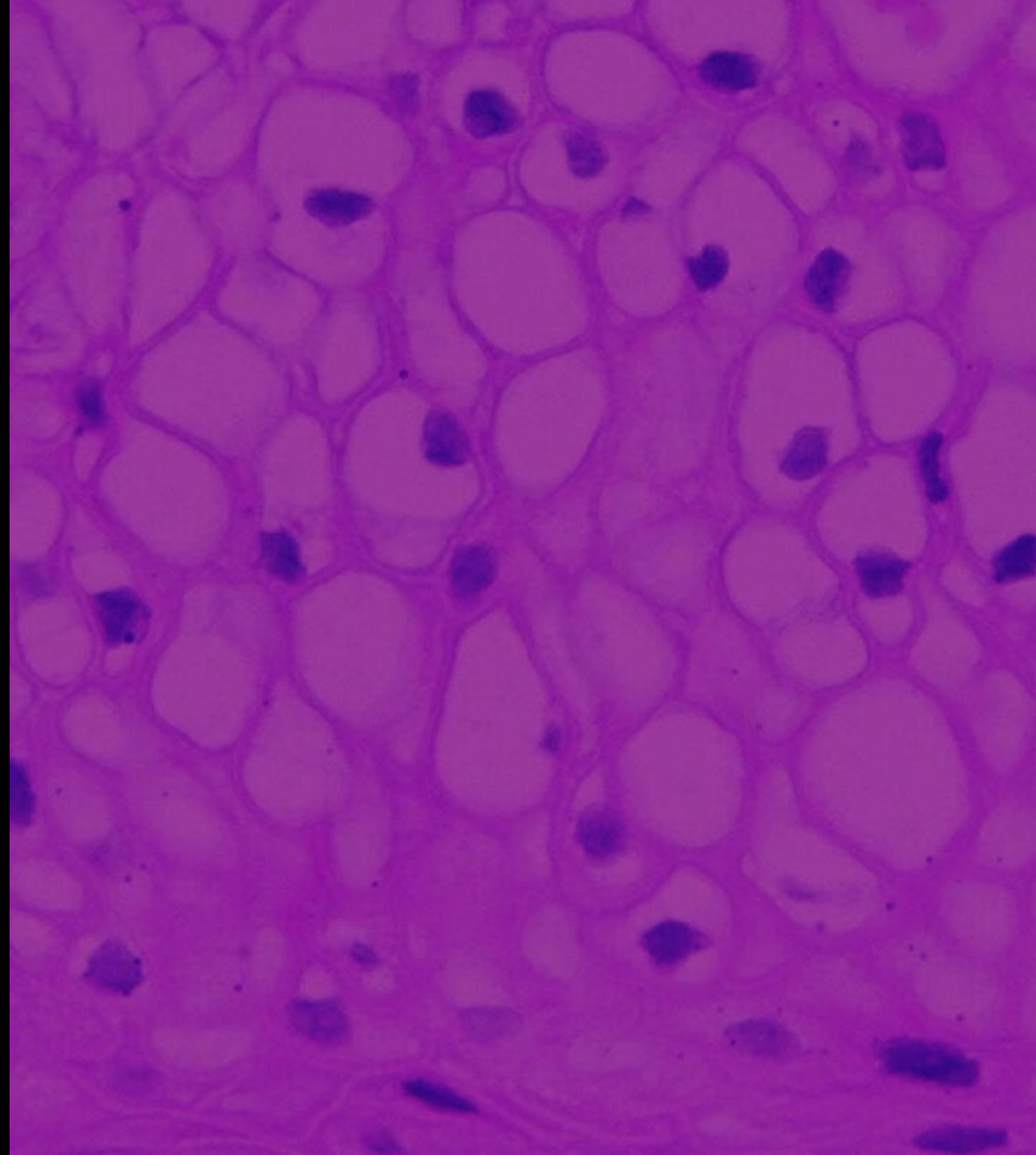
MATTEK

Now Part of Sartorius

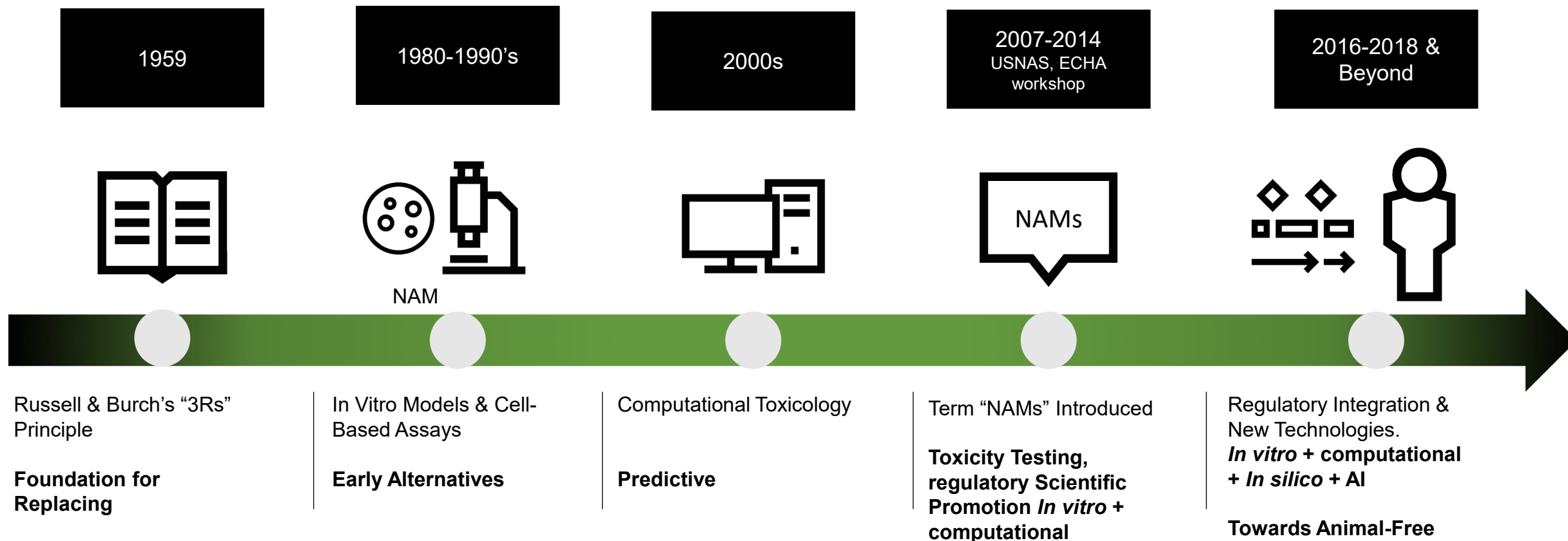
NAM Approach for Vaginal Irritation Assay to Evaluate Irritation Potential of Feminine Care Products and Medical Devices

Seyoum Ayehunie, Ph.D.

June 2026



Evolution from Cell Culture to NAMs



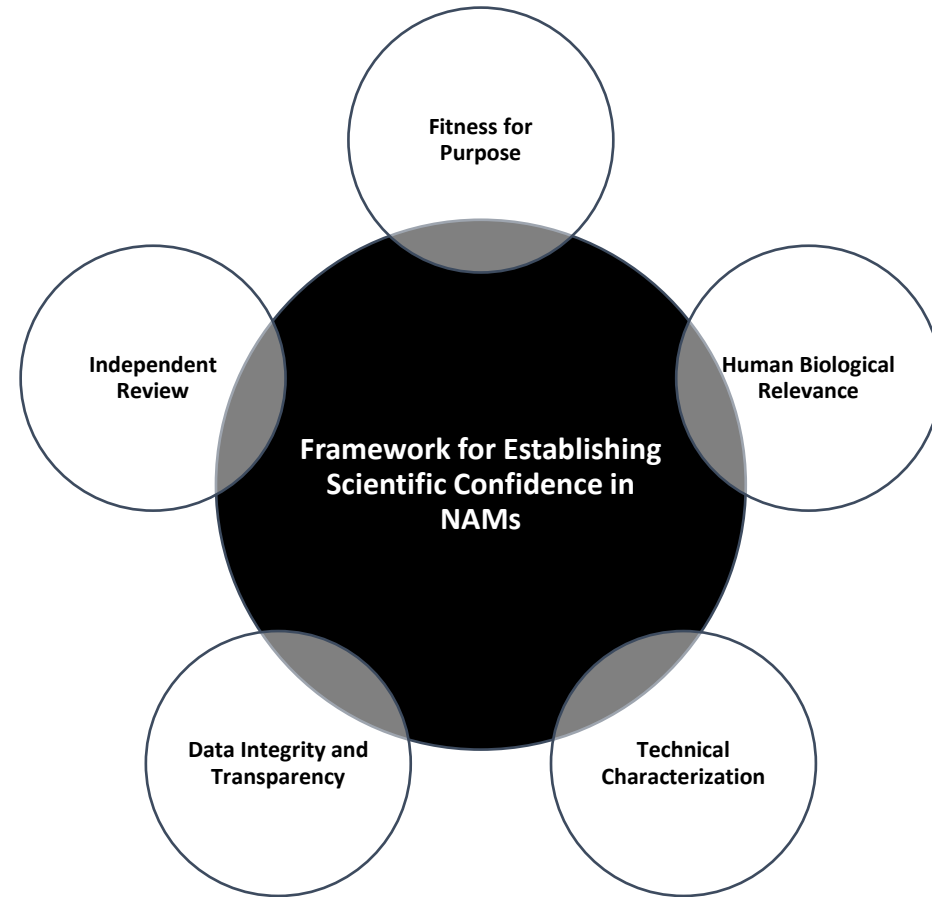
NAM = New Approach Methodology

What are NAMs?

- **Scientific & regulatory bodies:** Any Technology, methodology that can provide information on chemical hazard without using animals (In vitro, In silico, HTS)- Replacing animal testing.
- **Academia and Research:** Innovative scientific approaches that improve traditional animal testing (Mechanistic, organ-on-a-chip, integration of data sources – Better science.
- **Pharmaceutical Industry:** Efficient and cost-effective tools that reduce reliance on animal testing while supporting product safety and innovation. They value a) fast results, B) lower costs, 3) regulatory acceptance, and 4) reproducibility and scalability – Efficacy and compliance.
- **International collaboration initiatives:** Any non-animal alternative approach- computational, biochemical, cell-based methods, to assess safety or biological activity - standardization and validation of methods.
- **Animal welfare organizations:** Human alternatives that replace, reduce, or refine animal testing. They value ethical issues, elimination of animal suffering – Ethics and animal protection.
- → **Impetus within the community just now to standardise what is meant by “NAMs” to harmonise efforts**

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) - Core Principles

- An Inter-agency committee that coordinates safety
- Aims to reduce, refine, and replace animal use in testing programs
- ICCVAM works closely with NICEATM, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, which provides scientific and operational support for evaluating NAMs



Key Drivers for NAM Adoption



The draft guidance

FDA establishes four core validation principles for NAMs.



Context of Use

Clear definition of NAMs' intended regulatory purpose.



Human Biological Relevance

Demonstration of how NAMs can assess toxicity.



Technical Characterization

Establishment of scientific confidence through robust, reliable, and reproducible methods.



Fit-for-Purpose

Assurance that NAMs help in regulatory decision-making (e.g., drug review and potential approval).

Medical devices

- FDA classified medical devices into three categories
- FDA - Center for Devices and Radiological Health (CDRH) classifies personal lubricants as Class II medical devices.

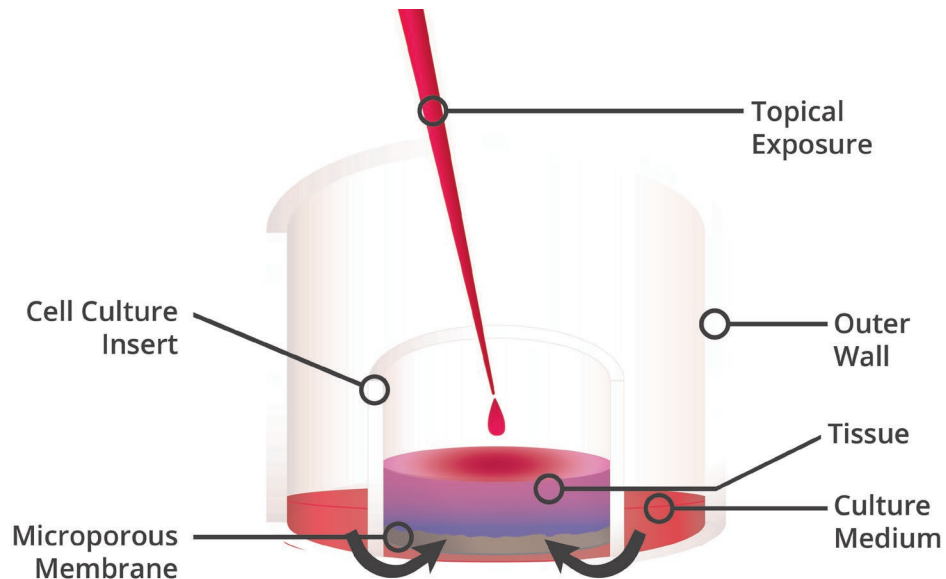
Risk-based
Classification of
Medical devices

Medical Device Classification				
Category	Device Human Risk	FDA Requirement	510(k) premarket notification exemption	Compliance Requirement
Class I	Low	General Control	Yes	Registration, labeling, and good manufacturing practices
Class II	Moderate	Special Control	Yes	Performance standards, postmarket surveillance, or special labeling
Class III	High	Premarket Approval	No	FDA approval before commercial distribution. Demonstration safety and effectiveness

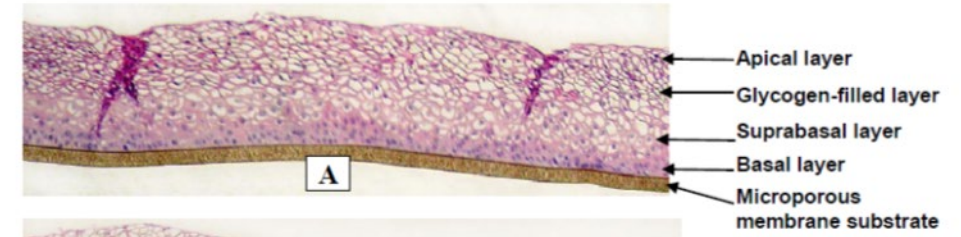
A Consortium comprising the Institute for In Vitro Sciences, Inc. (IIVS), industry, the Consumer Healthcare Products Association (CHPA), and the PETA International Science Consortium (PETA-ISC) is qualifying the use of an in vitro testing method as replacement for the RVI test.

A research plan has been accepted into the FDA CDRH Medical Device Development Tools (MDDT) program as a potential non-clinical assessment model (NAM).

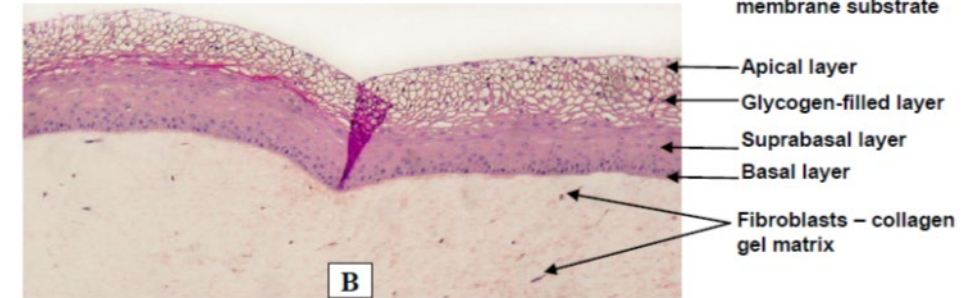
EpiVaginal to Evaluate Product Safety



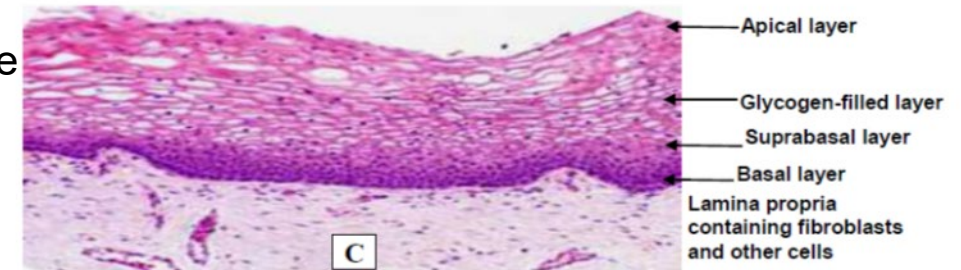
A) EpiVaginal



B) EpiVaginalFT



C) Explant Tissue



Histology comparison of: EpiVaginal **A)** EpiVaginal-100 (VEC-100) **B)** Epi-Vaginal-full thickness (VEC-100-FT) and **C)** Vaginal (human) explant tissues.

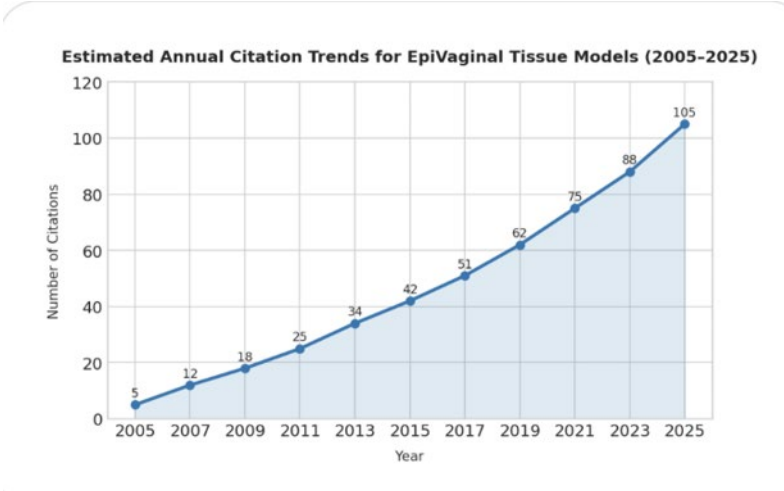
→ EpiVaginal tissues mimic morphology of explant vaginal tissues.

Reproducibility of EpiVaginal Microtissues

Location	Year	AVG ET-50 (h)	St Dev (h)	Avg Exp CV(%)	# of tissues lots
US	2024	1.0	8.2	8.2	20.0
Slovakia	2024-2025	1.4	9.3	9.3	31.0
US-historical	2006-2007	1.1	9.1	9.1	46.0

Table 1: Reproducibility of EpiVaginal tissue lots produced at Mattek (US) in 2024 and at Mattek Europe (Slovakia) during 2024-2025. Results were compared to the historical QC data available from 2006-2007. The average experimental coefficient of variation (Avg Exp CV), a measure of Intralot variability of the tissues, is low (<10).

- **Regulatory acceptance:** Not formally Validated but FDA acceptance on a Case-by-Case basis for cytotoxicity of lubricants.



Analysis of the Citation Curve

Irritation Testing Using EpiVaginal

Product Category	Lowest ET-50 (hr)	Highest ET-50 (hr)	# of products tested
Feminine washes	1.8	2.7	3
Spermicides	3.9	6.7	4
Anti-itch creams	6.8	>18	4
Anti-fungal agents	38.7	>48	3
Personal lubricants	>18	>48	2
Douche	>18	>48	2

Ayehunie, S., *et al.* Organotypic human vaginal-ectocervical tissue model for irritation studies of spermicides, microbicides, and feminine-care products. *Toxicology in Vitro*, 20, (5), 689-698, (2006).

Dover, S.E., Safety study of an antimicrobial peptide lactocin 160, produced by the vaginal lactobacillus rhamnosus. *Infect. Dis. in Obst. and Gynec.*, 78248, 1-6 (2007).

In vivo vs *In vitro* comparison

Table: Summary of results from in vitro and in vivo studies using 14 blinded test articles

Test Chemical	<i>In vivo</i>	<i>In vitro</i>			
	RVI Score	MTT Viability		TEER	
		%	SD	%	SD
Saline	1-2	100.0	0.0	100.0	0
Maltose	1	94.3	9.1	98.7	5.6
Nonoxynol 9 (N9)	2-3	6.5	1.4	7.4	2.5
Beta Cyclodextran	2	102.0	17.9	94.4	4.5
Benzalkonium chloride	14	11.7	4.6	9.7	6.3
Adonitol	3	94.7	11.9	100.3	5.4
Aluminum sulfate	2	102.4	5.1	145.3	23.5
Sodium bicarbonate	2	98.1	14.2	96.7	8.9
Lactic acid	3	73.7	10.0	118.08	35.3
Betadine	4	96.6	5.3	91.4	7.9
Copper sulfate	3	9.4	4.6	61.9	29.1
Diacetin	2	97.4	11.5	96.7	12.4
Sodium dodecyl sulfate	3	4.7	0.9	8.8	6.6
Dulcitol	3	97.2	3.9	96.9	10.3
Sham/untreated control	1	111.3	6.8	119.5	8.0
Irritating					

Data Integrity and Transpare

Development of an in vitro alternative assay method for vaginal irritation

Seyoum Ayehunie ^a✉, Chris Cannon ^a, Karen LaRosa ^a, Jeffrey Pudney ^b, Deborah J. Anderson ^b, Mitchell Klausner ^a

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https://doi.org/10.1016/j.tox.2010.10.001

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Abstract

The vaginal mucosa is commonly exposed to chemicals and therapeutic agents that may result in irritation and/or inflammation. In addition to acute effects, vaginal irritation and inflammation can make women more susceptible to infections such as HIV-1 and [herpes simplex virus 2](#) (HSV-2). Hence, the vaginal irritation potential of feminine care formulations and vaginally administered therapeutic agents is a significant public health concern. Traditionally, testing of such materials has been performed using the rabbit vaginal irritation (RVI) assay. In the current study, we investigated whether the organotypic, highly differentiated EpiVaginal™ tissue could be used as a non-animal alternative to the RVI test. The EpiVaginal tissue was exposed to a single application of ingredients commonly found in feminine hygiene products and the effects on tissue viability (MTT assay), barrier disruption (measured by transepithelial electrical resistance, TEER and [sodium fluorescein](#) (NaFl) leakage), and inflammatory cytokine release (interleukin (IL)-1α, IL-1β, IL-6, and IL-8) patterns were examined. When compared to untreated controls, two irritating ingredients, nonoxynol 9 and benzalkonium chloride, reduced tissue viability to <40% and TEER to <60% while increasing NaFl leakage by 11–24% and IL-1α and IL-1β release by >100%. Four other non-irritating materials had minimal effects on these parameters. Assay reproducibility was confirmed by testing the chemicals using three different tissue production lots and by using tissues

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same donor or lots reconstructed with cells obtained from different donors were less than 10% and 12%, respectively. In conclusion, decreases in tissue viability and barrier function and increases in IL-1α and IL-1β release appear to be useful endpoints for preclinical screening of topically applied

► [Toxicol In Vitro](#). 2006 Aug;20(5):689-98. doi: 10.1016/j.tiv.2005.10.002. Epub 2005 Nov 23.

Organotypic human vaginal–ectocervical tissue model for irritation studies of spermicides, microbicides, and feminine–care products

Seyoum Ayehunie ¹, Chris Cannon, Sarah Lamore, Joseph Kubilus, Deborah J Anderson, Jeffrey Pudney, Mitchell Klausner

Affiliations + expand
PMID: 16309879 DOI: [10.1016/j.tiv.2005.10.002](#)

Abstract

A three-dimensional organotypic vaginal-ectocervical (VEC) tissue model has been developed to test the irritation of topically applied spermicides, microbicides, and vaginal-care products. The in vitro tissue model was reconstructed using normal VEC epithelial cells and is well stratified, containing differentiated basal, suprabasal, intermediate, and superficial cell layers similar to in vivo tissue. The intermediate and superficial cell layers contain glycogen, and the expression of cytokeratins 13 and 14 in the tissue also parallels that of native tissue. The MTT viability assay and histological assessment were used to test inter-lot and intra-lot reproducibility. The MTT average intra-lot coefficient of variation (CV) was less than 10% and the time required to reduce tissue viability by 50% (ET-50) following application of 1% Triton X-100 averaged 1.25+/-0.24h (n=23) upon completion of the 11-day culture period and 1.30 h+/- 0.19 for the same tissues stored overnight at 4 degrees C on agarose gels. The utility of the VEC model for irritation studies was examined by testing commercially available

International Journal of Antimicrobial Agents 50 (2017) 171–176

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International Journal of Antimicrobial Agents

journal homepage: [www.elsevier.com/locate/ijantimicag](#)

Blocking and dislocation of *Candida albicans* Cdr1p transporter by styrylquinolines

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^a Faculty of Biotechnology, University of Wrocław, Wrocław, Poland
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ARTICLE INFO

Article history:
Received 22 September 2016
Accepted 30 January 2017

Keywords:
Candida albicans
Cdr1p
Styrylquinolines
ABC transporters
Drug design

ABSTRACT

Styrylquinolines are a novel group of quinoline drugs that are known to have antiproliferative activity and antiviral properties. This study evaluated the antifunga drugs more deeply, particularly their activity modulation towards Cdr1p, the main m er of *Candida albicans*. Styrylquinolines were found to have antifungal activity and to w with fluconazole. Additionally, they decreased the extracellular concentration of rhod transporter-expressing cells. The cellular localization of GFP-tagged Cdr1p was assessed microscopy. Styrylquinolines induce expression of Cdr1p, as confirmed by Western blot drugs tested caused the partial delocalization of transport protein to the cytoplasm. T the first evidence that styrylquinolines decrease the activity of ABC multidrug transpo © 2017 The Authors. Published by Elsevier B.V. This is an open access article under license ([http://creativecommons.org/licenses](#)

Toxicology in Vitro 112 (2020) 106198

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Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: [www.elsevier.com/locate/toxinvit](#)

Using a reconstructed human vaginal epithelium model to assess irritation: A proof-of-concept study supporting regulatory qualification of the method for use with personal lubricants

Jessica Perrin ^{a,*}, Gertrude-Emilia Costin ^b, Seyoum Ayehunie ^c, Helena Kandarova ^{d,e}, Timothy Landry ^c, Jeffrey Brown ^a, Amy J. Clippinger ^a

^a PETA Science Consortium International c.V., Friedhelm-Straße 3, 70499 Stuttgart, Germany
^b Institute for In Vitro Sciences, Inc., 30 W Watkins Mill Road, Suite 100, Gaithersburg, MD 20878, USA
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ARTICLE INFO

Editor: Dr. I Macchusneyer

Keywords:
Vaginal irritation
Lubricants
ISO
Reconstructed human vaginal epithelium
Biocompatibility
In vitro

ABSTRACT

Consumers tend to think of personal lubricants as personal care products or cosmetics that are not tested using animals, but the regulatory classification and hence the testing requirements for these products vary by country. For example, in the United States, regulations and guidance classify personal lubricants as medical devices, for which manufacturers must perform a rabbit vaginal irritation (RVI) test as part of a typical safety assessment submitted to the Food and Drug Administration (FDA). This publication discusses replacing the RVI with an in vitro reconstructed human vaginal epithelium (RHIVE) test method, which uses the EpiVaginal model to assess the irritation potential of personal lubricants. The proof-of-concept studies presented here indicate that this in vitro test method can rank water-based personal lubricants by vaginal irritation potential. Scientific confidence in this test method is evaluated based on an established framework that considers the method's context of use, human biological relevance, technical characterization, data integrity and transparency, and independent review. A proposed workplan aims to further develop and qualify the in vitro test method for regulatory acceptance in assessing vaginal irritation of personal lubricants, and expanding its use to other products.

Acknowledgments

Boston Medical Center, Boston, MA

J. Pudney

D. Anderson

Grant Support:

NIAID & NICHD, NIH



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29 June 2026

ESTIV International Congress

In Vitro Irritation Testing of Medical Devices

Kelly Coleman, PhD, DABT, ERT, ATS, RAC
Sr. Distinguished Toxicologist
Medtronic plc



LEGAL DISCLAIMER

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

The presenter has no conflicts of interest.

kelly.p.coleman@medtronic.com

MEDICAL DEVICE TOXICOLOGY

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**



IN VITRO IRRITATION TIMELINE

2009 – Research Begins at Medtronic

2010 – ISO/TC 194 Meeting in Berlin

2012 – Pilot Project Completed

2017 – Round Robin Study Completed

2019 – Follow-Up Study Completed

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

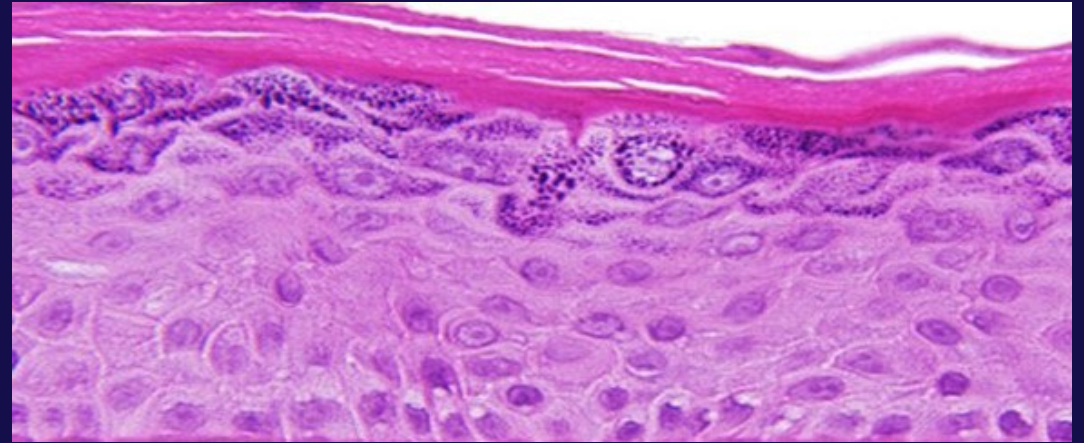
2021 – EN ISO 10993-23 Published in OJEU (July)

2025 – ISO 10993-23 Amended (May)



ROUND ROBIN STUDY (2012 – 2017)

- ISO/TC 194 **Working Group 8** Task Force
- **24 laboratories** around the world
- **2,000** blinded polymer samples
- Tissues: **EpiDerm SIT & SkinEthic RHE**
- Published in special issue of ***Toxicology In Vitro*** (De Jong et al., 2018)



EpiDerm™, MatTek Life Sciences

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.

The screenshot shows the ISO website page for the standard ISO 10993-23:2021. The page is titled "ISO 10993-23:2021 Biological evaluation of medical devices — Part 23: Tests for irritation". The breadcrumb trail is "ICS > 11 > 11.100 > 11.100.20". The page includes an "ABSTRACT" section with a "PREVIEW" button. The abstract text states: "This document specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation. The tests are designed to predict and classify the irritation potential of medical devices, materials or their extracts according to ISO 10993-1 and ISO 10993-2." Below the abstract, it lists the contents: "This document includes: — pre-test considerations for irritation, including *in silico* and *in vitro* methods for dermal exposure; — details of *in vitro* and *in vivo* irritation test procedures; — key factors for the interpretation of the results." The "GENERAL INFORMATION" section provides details: "Status : © Published", "Publication date : 2021-01", "Corrected version (fr) : 2021-02", "Edition : 1", "Number of pages : 60", "Technical Committee : ISO/TC 194 Biological and clinical evaluation of medical devices", and "ICS : 11.100.20 Biological evaluation of medical devices". On the right side, there is a "BUY THIS STANDARD" section with a table for "FORMAT" and "LANGUAGE". The table shows "PDF + EPUB" selected for the format and "English" for the language. The price is listed as "CHF 178" with a "BUY" button.

ISO

Standards About us News Taking part Store

ICS > 11 > 11.100 > 11.100.20

ISO 10993-23:2021

Biological evaluation of medical devices — Part 23: Tests for irritation

ABSTRACT [PREVIEW](#)

This document specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation. The tests are designed to predict and classify the irritation potential of medical devices, materials or their extracts according to ISO 10993-1 and ISO 10993-2.

This document includes:

- pre-test considerations for irritation, including *in silico* and *in vitro* methods for dermal exposure;
- details of *in vitro* and *in vivo* irritation test procedures;
- key factors for the interpretation of the results.

GENERAL INFORMATION

Status : © Published Publication date : 2021-01
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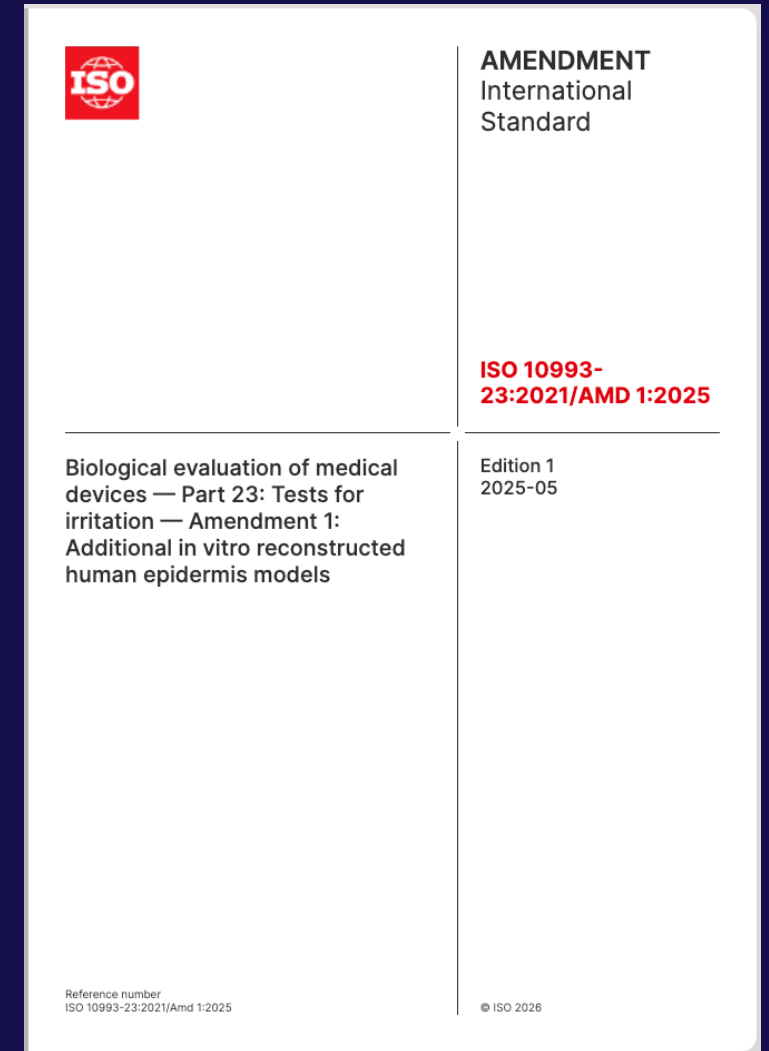
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FORMAT	LANGUAGE
✓ PDF + EPUB	English
PAPER	English

CHF 178 [BUY](#)

FOLLOW-UP STUDIES

- Comparison of **in vitro** and **in vivo** results (De Jong et al., 2020).
- In vitro irritation testing of **mild irritants** and **non-extractables** (Pellevoisin et al., 2022).
- Round robin study of **LabCyte EPI-MODEL24 SIT** tissues (Japan, 2024).
- Round robin study of **KeraSkin SIT** tissues (Kim et al., 2024).
- **May 2025: ISO 10993-23 amended** to include Korea's **KeraSkin** and Japan's **LabCyte** tissues.



GLOBAL ACCEPTANCE (2025)

- 191 (99%) of the UN's 193 Member States directly or indirectly recognize ISO 10993-23:2021 and accept in vitro irritation testing data.
- 95% of humanity lives in those 191 countries.
- Recognition by the US and Canada is pending.



ONGOING EFFORTS (2026)

- Addressing **US FDA's concerns** with RhE tissues.
- Resubmitted **MDDT** proposal to US FDA.
- **Data-mining** for rabbit irritation testing results.
- Collection of **dual-data** from CROs and industry.
- Possible limited follow-up with RhE tissue testing.

IN VITRO IRRITATION SUMMARY

- ✓ We've come along way from the ISO meeting in Berlin.
- ✓ **Lessons learned** have been adopted by NAMs developers.
- ✓ **Near universal global** acceptance has been achieved.
- ✓ Additional work may convince FDA to accept in vitro data.

Advancing medical device pyrogen testing through the in vitro monocyte activation test

MAT BioTech

MAT BioTech

MAT BioTech's mission is to pioneer the advancement of in vitro pyrogen tests that replace animal based incumbents, supporting the safe development and release of parenteral products. MAT BioTech offers the field's leading MAT assay kit & certified MAT CRO services to leading parenteral manufacturers worldwide.

Shabnam Solati, Chief Scientist

A key opinion leader and subject matter expert in the MAT field, Shabnam has authored numerous academic publications and spearheaded the MAT's development, commercialisation and adoption in the field worldwide, since 2005.

Shabnam Solati
shabnam@mat-biotech.com

1. Introducing pyrogen testing

1.1. What are pyrogens?

Substances which may induce fever (i.e., a rise in body temperature) when introduced into the human body ([Kluger, 1991](#); [Moltz, 1993](#)).

1.2. Why is pyrogen testing important?

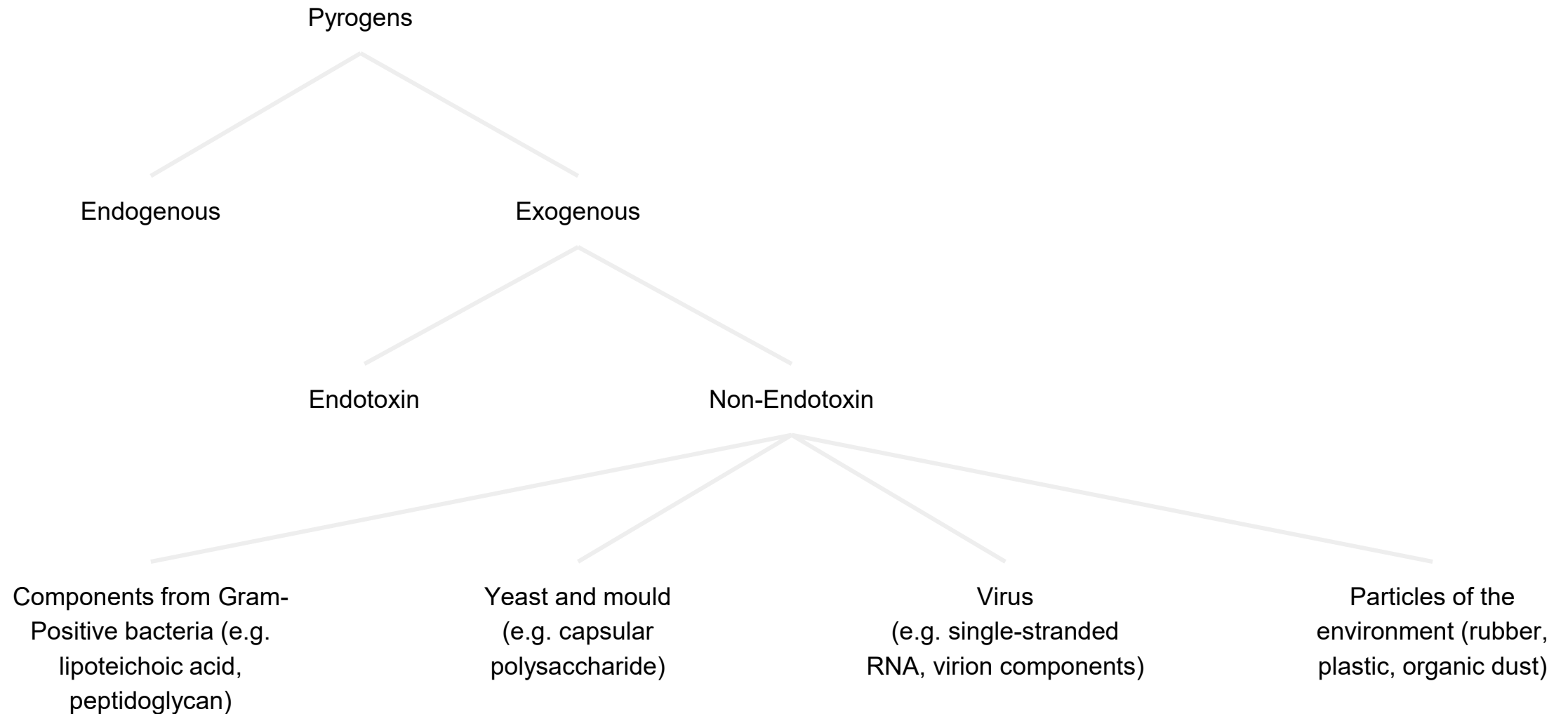
Beyond fever: shock, severe inflammation, multiple organ failure and even death ([Hasiwa, 2013](#), [Hartung et al., 1997](#); [Dinarello, 2000](#); [Beutler et al., 2003](#)). For parenteral medicines; detection is essential to ensure safety prior to patient administration ([Ding and Ho, 2001](#)).

1.3. Human immune response to pyrogens

Pyrogens bind to toll-like receptors (TLRs), leading to activation of intracellular pathways. Cytokines (e.g., IL-6, IL-8, IL-1 β , TNF- α) are resultantly produced and secreted into the bloodstream; travel to the hypothalamus which responds by raising the body's temperature.

1. Introducing pyrogen testing

1.4. Diversity of pyrogens



2. Pyrogen detection assays for medical devices

2.1. Rabbit Pyrogen Test (RPT)

In vivo pyrogen test that measures the febrile response of rabbits as an end point. Specifically, a saline extract from a medical device or its materials is injected into the ear of a rabbit – If pyrogens are present, the rabbit’s temperature will rise above a specific threshold and the test will fail.

Strengths	Weaknesses
Specificity (Nakagawa et al., 2002)	Animal harm
	Low biological relevance (Greisman and Hornick, 1969)
	Qualitative results: (Bellentani, 1982).
	Low sensitivity (Schindler et al., 2003 , 2009).
	Interference prone (Schindler et al., 2009)
	Solid sample restrictions (Mazzotti et al., 2006 ; Gimenes et al., 2024)
	Extraction inefficiencies (Mazzotti et al., 2006)

2. Pyrogen detection assays for medical devices

2.2. Bacterial endotoxin test (BET)

The bacterial endotoxin test is an ex vivo endotoxin test that detects pyrogenicity by operationalising the horseshoe crab (Limulus polyphemus) blood clotting reaction when exposed to the presence of bacterial endotoxins

Strengths	Weaknesses
Quantitative results (Weary et al., 1980)	No non-endotoxin pyrogen detection (spore formers) (Morath et al., 2002a ; Schindler et al., 2009)
High sensitivity (0.005 EU/mL LPS)	Low biological relevance (Spreitzer et al., 2002 ; Williams, 2001)
Cost effectiveness	Interference prone cascade (Cooper et al., 1997 ; Duner, 1995)
	Animal harm (Rudloe and Hernkind, 1983) – recombinant alt. available
	Solid sample restrictions (Ross and Bruch, 1982 ; Roslansky et al., 1991)
	Extraction inefficiencies (Mazzotti et al., 2006)

2. Pyrogen detection assays for medical devices

2.3. Human cell-based pyrogen test (HCPT) a.k.a. Monocyte activation test (MAT)

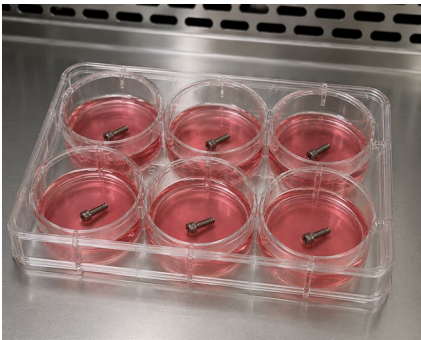
The Monocyte Activation Test (MAT) is an in vitro pyrogen test that detects fever-inducing endotoxins and non-endotoxin pyrogens in parenterals by measuring the immune response of human monocytes.

Strengths	Weaknesses
Minimize animal harm	Pricing
High biological relevance	
High specificity	
High sensitivity	
Interference averse	
Quantitative data generation	
Can test solid samples	

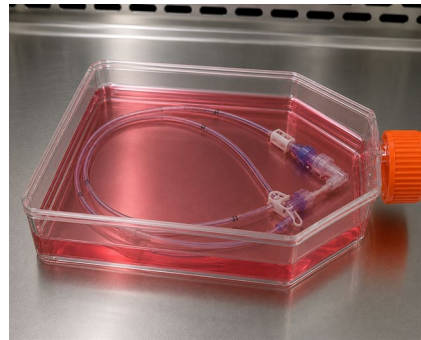
2. Pyrogen detection assays for medical devices

2.3. Human cell-based pyrogen test (HCPT) a.k.a. Monocyte activation test (MAT)

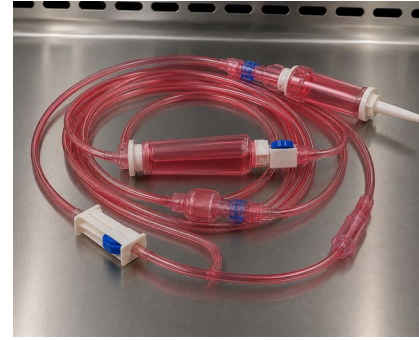
Direct device-to-cell analytical set-up



Dental Screw (6-15 mm)



PICC line (40-65 cm)



Transfusion Set (150–180 cm)

Dynamic incubation



3. European leadership towards NAM application in pyrogen testing

3.1. Ph. Eur. chapter 2.6.30. Monocyte-activation test

Ph. Eur. General chapter 2.6.30. *Monocyte-activation test* describing product-specific validation (preparatory testing) requirements as well as two routine testing methodologies: method 1 semi-quantitative test & method 2 reference lot comparison test.

3.2. Removal of RPT

Commitment towards 3Rs (Replace, Reduce, Refine), 1 January 2026: European Directorate for the Quality of Medicines & Healthcare (EDQM) removed RPT from 57 revised texts.

3.3. Introduction of *new* Ph. Eur. chapter 5.1.13 Pyrogenicity

Delineates pyrogen test selection: MAT as NEP risk assessment during development of production process of if any changes made that influence the quality of the product with regard to pyrogenicity:

- Where NEP risk ruled out, BET as routine test;
- Where NEP risk not ruled out: MAT as routine test;
- Where NEP risk ruled out, but BET unsuitable: MAT as routine test

3. European leadership towards NAM application in pyrogen testing

3.4. International NAM (MAT) transition for drug testing

United States Pharmacopeia (USP)	General Chapter <151> Pyrogen Test “A validated, equivalent in vitro pyrogen or bacterial endotoxin test may be used in place of the in vivo rabbit pyrogen test, where appropriate .”
Food and Drug Administration (FDA)	Guidance For Industry Pyrogen and Endotoxins testing: Questions and Answers , may use alternative assays to those in the USP for a compendial article, e.g., Monocyte Activation Test, “if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, and in other special circumstances”. <ul style="list-style-type: none">• Such assays should be validated according to USP General Chapter <1225> Validation of Compendial Procedures and “should be shown to achieve equivalent or better results.”• Product-specific validation is necessary and should include interference testing and accurate detection of pyrogens in test samples.
Indian Pharmacopoeia (IP)	General Chapter 2.2.25 MAT (2018): guidelines for MAT use as RPT replacement where feasible
Japanese Pharmacopoeia (JP)	Monocyte-Activation Test as an Alternative Method for Pyrogen Test" (G4-13-190) acknowledges MAT as potential alternative to RPT.
Farmacopéia Brasileira	Farmacopéia Brasileira (ANSIVA) 7th Edition in 2024: MAT an alternative approach to the RPT for vaccines, blood-derived products and other medicines.

4. Medical devices falling behind in application of MAT as NAM

4.1. ISO/TR 21582 (2021) shortfalls

Accepts MAT as a *useful alternative* in *some cases*; ISO TR 21582 in its current form has been left behind in its understanding of MAT, as well as its application. Significant points of improvement in recognition of MATs:

- Ability to detect all pyrogens as capably (or better) as RPT;
- Capability as pyrogen test across *all* product categories (e.g., also tissue-engineered products containing living cells that release cytokines and chemokines)
- Suitability for routine QC testing of large finished, sterilized products/devices
- Field-recognised strengths and weaknesses across cell sources & configurations
- Long understood overcoming of donor-dependant response through pooling
- Endotoxin equivalent unit (EEU) measures and interpretation of results
- Fundamental difference to BET

4.2. Paucity of published lab-based research in MAT medical device application over the past 5 years

4.3. Limited (free) access to subject matter expertise (SME)

Increasing MAT vendors, but remaining application complexity (no one-size fit-all approach) and lack of ubiquitous access to SME. Outsourcing leads to very high cost burden, leading to more obstacles. Need for open access support.

Example: Launch of “OpenAccess MAT” initiative to offer free & open access:

- Application support
- SME knowledge bank

Cooperative next actions

- Follow-through on 3Rs, opt & implement HCPT (MAT) despite “alternative” status
- Incorporating SME on HCPT (MAT) in TR drafting
- Published, peer reviewed MAT & medical device application research
- Call for Free & open access application support & SME knowledge bank

Introduction



Lindsey K. Borton, M.P.H., DABT
Principal

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Advocate for the use of evidence-based toxicology for medical device safety assessments.



Toxicology and biocompatibility consultant at Gradient (USA). Previously, I was an industry toxicologist for 12 years at small and large medical device companies. I help clients develop the necessary biological safety data for their device.



Active member of: Association for the Advancement of Medical Instrumentation (AAMI); International Organization for Standardization (ISO); Society of Toxicology (SOT); SOT Medical Device & Combination Product Specialty Section (MDCPSS).

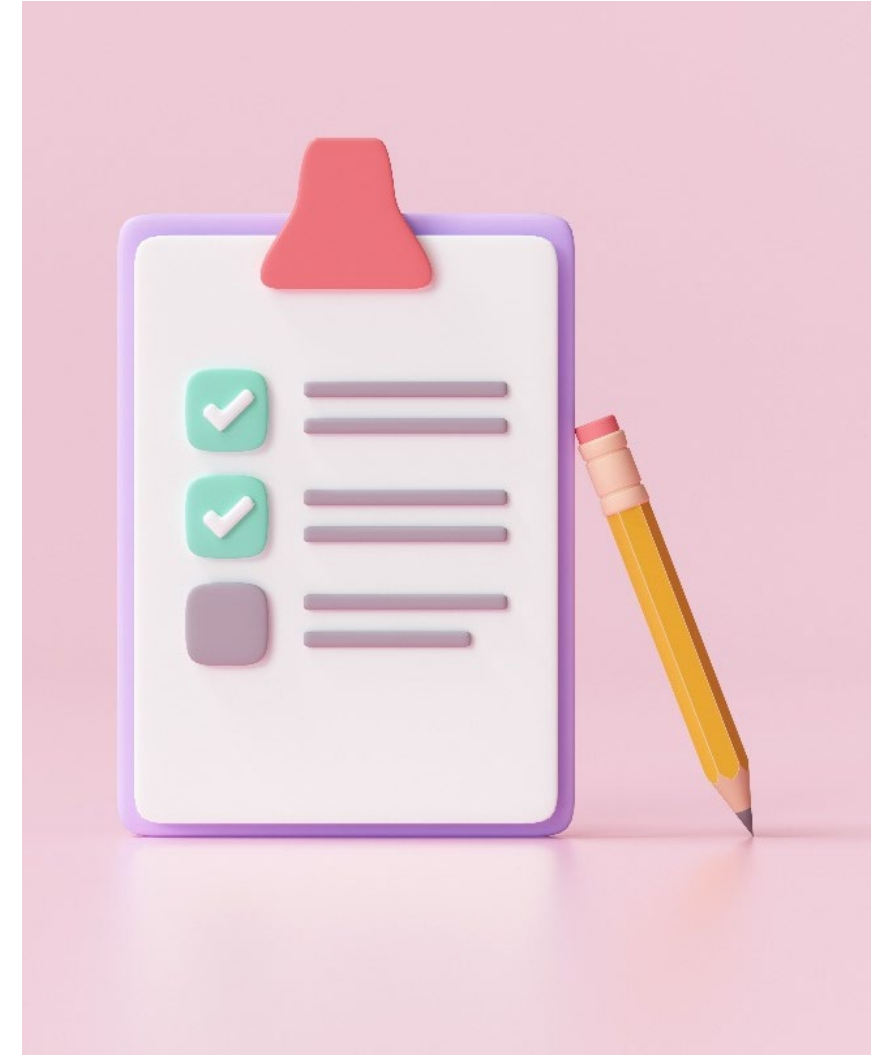
Chasing Phantoms?

A Case Study on Replacing the Rabbit Pyrogen Test for the Evaluation of Material-Mediated Pyrogens in Medical Devices

Lindsey K. Borton, M.P.H., DABT

Background: Medical Device Biological Safety Evaluation

- **"Material-mediated" pyrogens (MMP)** are believed to cause a **fever** when a patient uses a medical device
- **International Organization for Standardization (ISO)** produces a series of **standards or "rules"** that medical devices need to comply with to gain regulatory approval and then be used in people
- Current ISO standard states that the ***in vivo* rabbit pyrogen test (RPT)** is the **only** acceptable evaluation method
- Twentieth anniversary for RPT for medical devices
- So, we wanted to **change the rules...**



Material-Mediated Pyrogens in Medical Devices



Review Article

Material-Mediated Pyrogens in Medical Devices: Applicability of the *In Vitro* Monocyte Activation Test

Lindsey K. Borton¹ and Kelly P. Coleman²

<https://www.altex.org/index.php/altex/article/view/1027>



Review Article

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

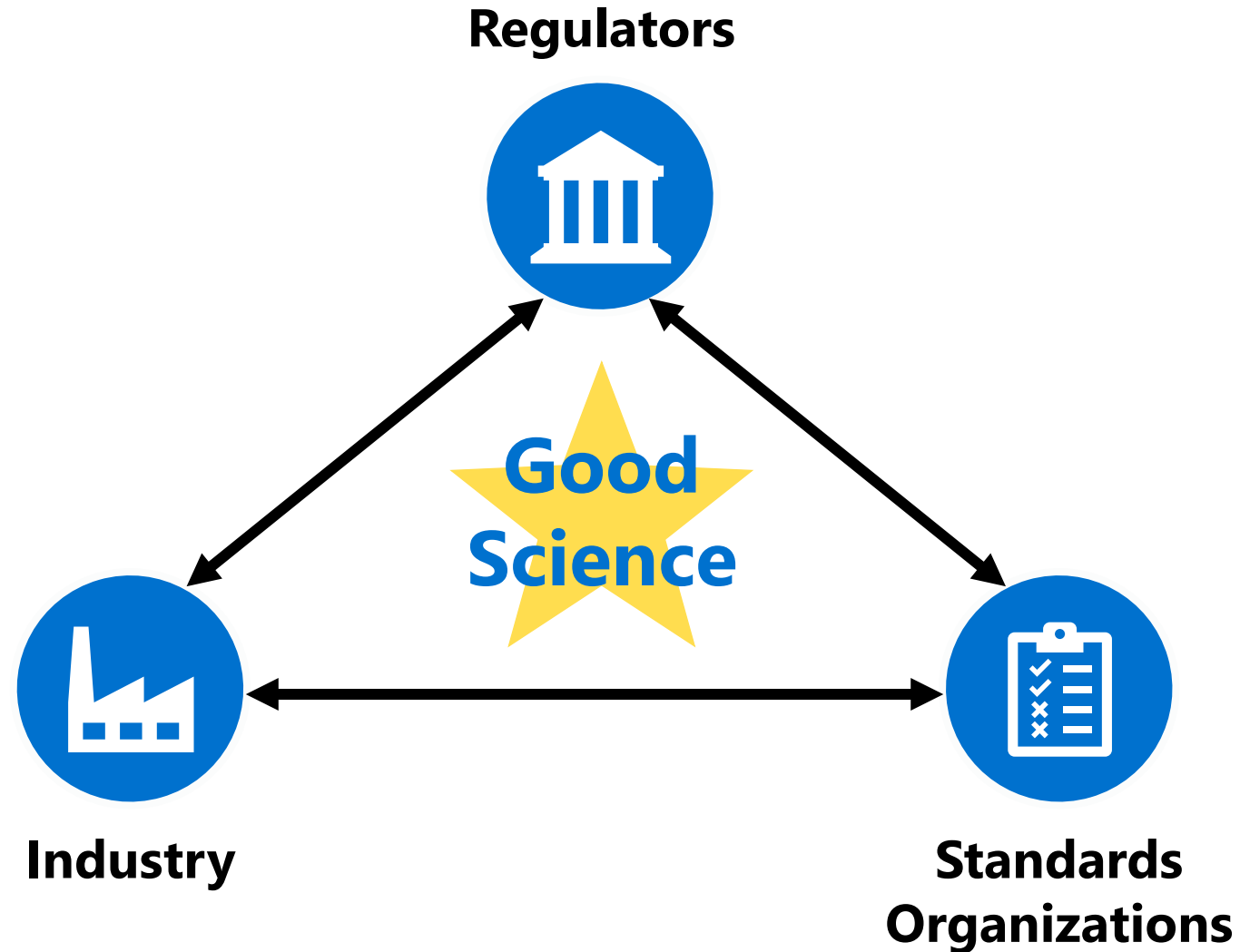
Lindsey K. Borton¹ and Kelly P. Coleman²

<https://www.altex.org/index.php/altex/article/view/2977>

Material-Mediated Pyrogens in Medical Devices: Key Findings

- The term "**material-mediated pyrogen**" (MMP) is **technically inaccurate. Eliminate it.**
- Of ~**18,300 medical device extracts**, only **2** substances suspected of having pyrogenic action (*neither* are actually pyrogenic)
- **91%** of identified **uncouplers are saline-insoluble**, so the RPT can't detect them
- **RPT** is **inadequate** and should be **immediately retired**

How to Change a Standard



- The research itself **did not catalyze change**
- But the data served as the bedrock we used to convince others that **change was overdue**

ISO at the International Level: Organization and Challenges

ISO Members

- European members = 19 votes
- Asian and Middle East members = 11 votes
- North American and South American members = 3 votes
- Each country gets one vote

Outcomes of this Framework

- ISO standards do not always reflect the diversity of national opinions
- If there is European Union (EU) consensus -> the standard goes into effect
- Increasing number of countries are not recognizing ISO standards, or are creating national guidelines (*e.g.*, US FDA's "Guideline on ISO 10993-1" and "Q&A on Pyrogen Testing")

ISO at the National Level Framework: Organization and Challenges

Europe Example:

- National bodies generally have **very few experts** that participate
- **Easy** to gain access to ISO level



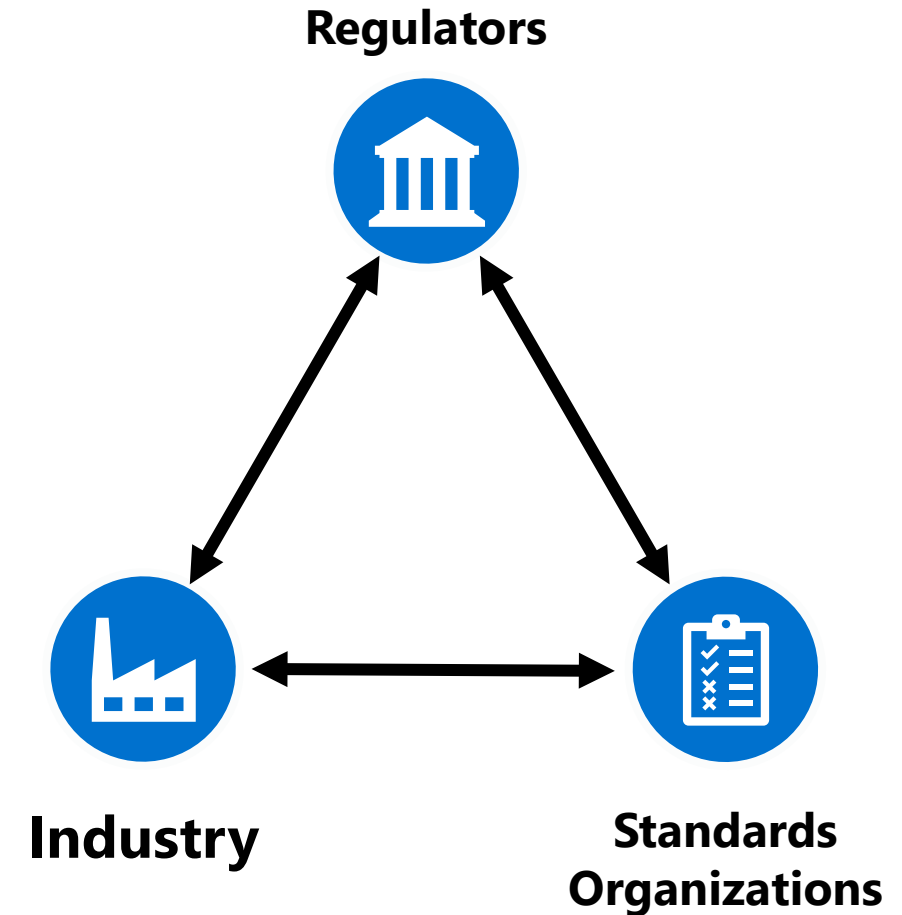
US Example:

- AAMI = 100+ companies and one US FDA
 - **Regulators have a very small voice** amongst many industry voices (*e.g.*, CROs, manufacturers, consultants)
- Extremely **competitive** to join at ISO level – many experienced experts unable to share expertise at international level



Eliminating the RPT from the ISO Medical Device Standards

- RPT removed from ISO 10993-1
 - EU votes overwhelmed other country votes
 - **Key RPT removal**
- RPT removed from draft ISO 10993-11
 - **US FDA currently requires the RPT** to approve a medical device for human use
 - At US national level, US FDA has one vote amongst many US votes; working with US FDA at national level
- **Outcome:**
 - RPT removed from key standard
 - RPT still required by regulators
 - **Need to go regulator-by-regulator to eliminate RPT**



Lessons Learned

- Holistic removal is a process that requires **international and national strategies**
- Advocate for direct **regulator** participation on ISO committees
- Take advantage of **EU voting power** in the ISO process!

YOUR Call to Action!

1. Identify where **your expertise** aligns in the ISO series

- Do you:
 - Have an expertise on validating *in vitro* methods?
 - Routinely interact with regulators?
 - Manufacture a product?

2. Then, **get involved!**

- Join national standards
- Provide comments and draft alternative texts for standards through your national body based on your expertise
- Join at the ISO level



Institute for **In Vitro** Sciences

Advancing Science & Animal Welfare Together



Amanda Ulrey, RQAP-GLP
Aulrey@iivs.org



President at the Institute for In Vitro Sciences, Inc., a non-profit research and testing laboratory dedicated to the advancement of in vitro (non-animal) methods worldwide.



Registered Quality Assurance Professional in Good Laboratory Practices (RQAP-GLP) since 2005. Elected member of the board of directors for the Society of Quality Assurance (SQA).



20+ years of experience designing and implementing quality systems for *in vitro* laboratories. Performs audits of validation data packets for data integrity assessments.

Member of: SQA, ASCCT, ESTIV



Converging Efforts to Advance NAM Adoption for Medical Device Safety

Collaborative progress enhancing safety in medical technology

Amanda Ulrey, RQAP-GLP

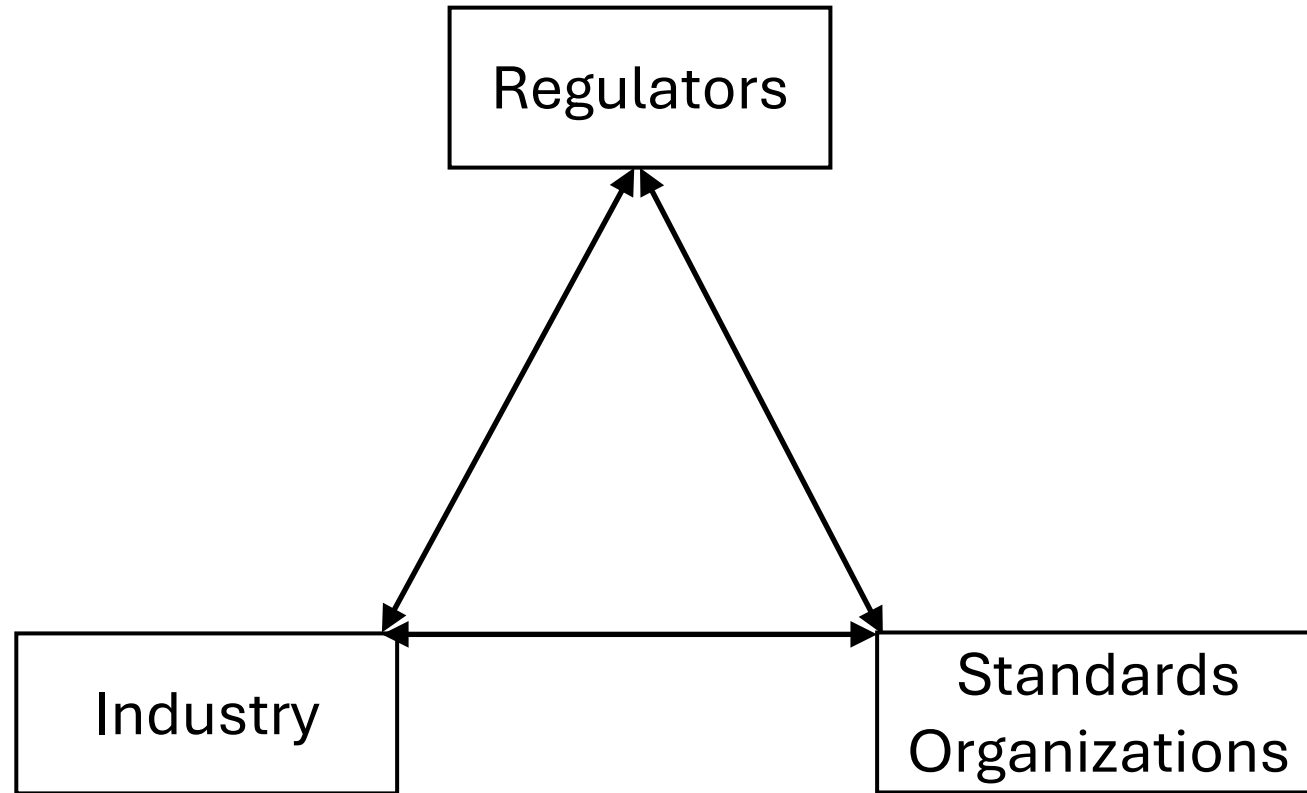
President, IIVS

&

Gertrude-Emilia Costin, PhD, MBA, ATS, ERT

Vice-President, Laboratory Operations, IIVS

The Awkward Triangle



The Quality Triforce

A focus on using quality standards and processes to improve data integrity and transparency strengthens the triangle and promotes scientific confidence.

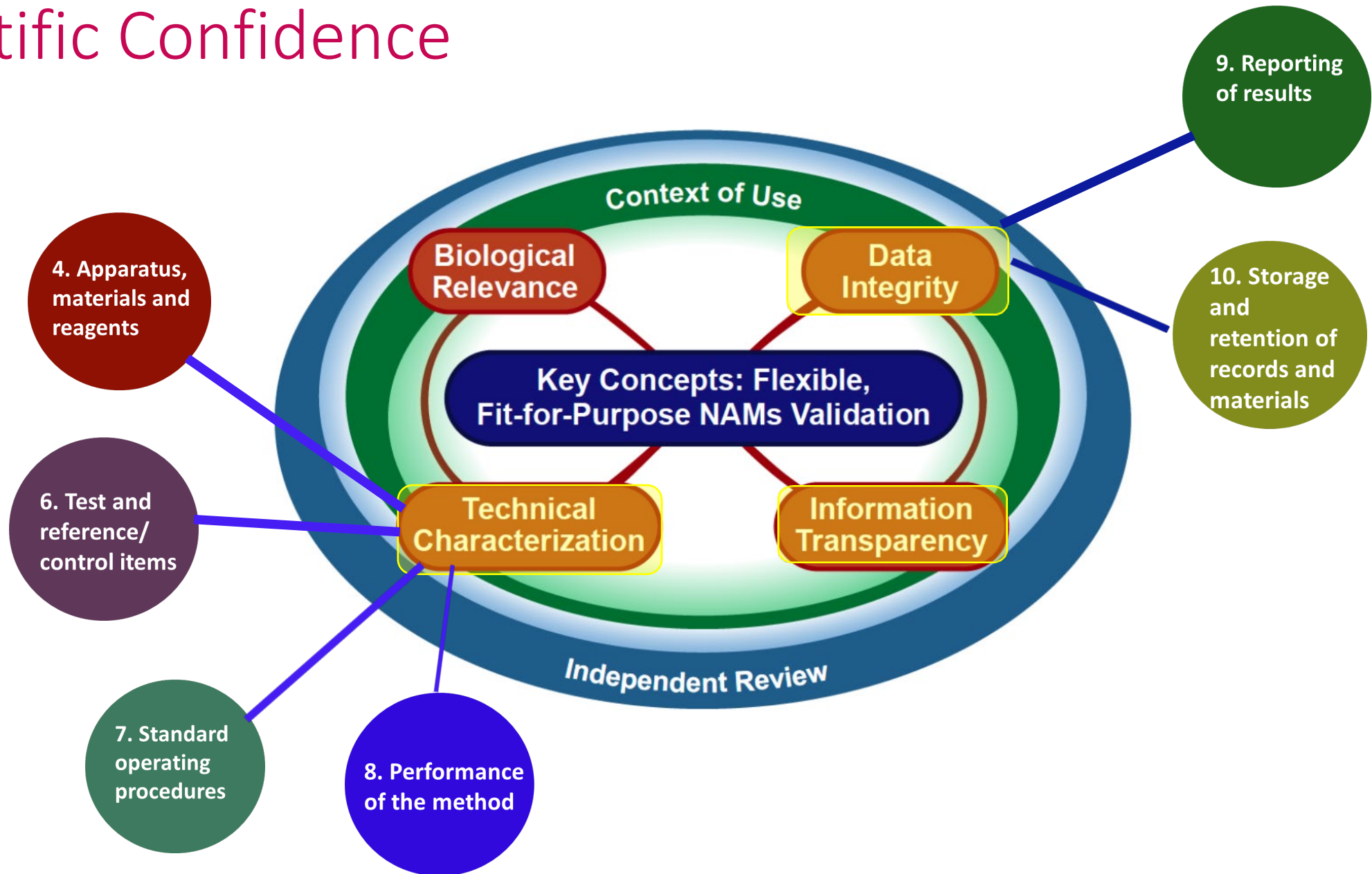


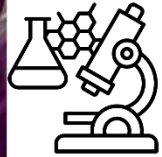
Good In Vitro Method Practices (GIVIMP)



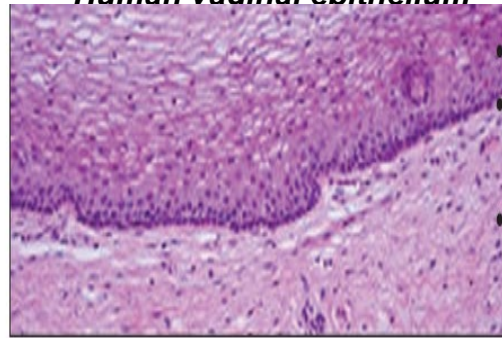
- 1) A detailed update on good practices for state-of-the-art *in vitro* methods applied to regulatory human safety assessment of a variety of compounds
- 2) Guidance to users and implementers of *in vitro* methods to help to ensure that methods are well-designed, robust, well-defined and well-described
- 3) Description of the key aspects that may impact the reliability and relevance of *in vitro* data
- 4) Description of the importance of reporting criteria, including establishing acceptance criteria and performance standards from *in vitro* data sets

Where GIVIMP Overlaps with the Framework for Scientific Confidence





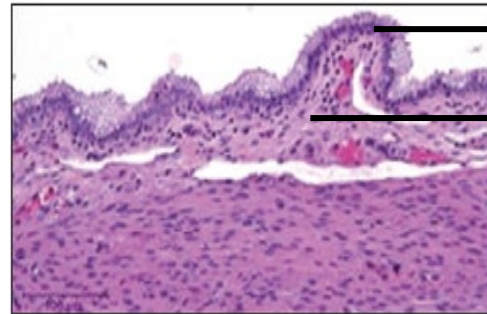
Human vaginal epithelium



suprabasal layer
basal layer
lamina propria
(containing fibroblasts
and other cell types)

**Stratified squamous
epithelium**

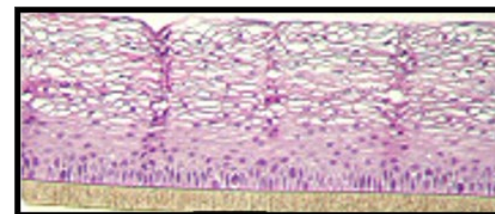
Rabbit vaginal epithelium



**Single layer of columnar
epithelial cells**

vaginal epithelial
layer
lamina propria
(sub-mucosal
layers)

Reconstructed human vaginal
mucosa (EpiVaginal™)
from MatTek Corporation



Normal vaginal ecto-cervical
epithelial cells

Fitness for Purpose

Human
Biological
Relevance

Technical
Characterization

Framework for Establishing
Scientific Confidence in NAMs

Independent Review

Data Integrity
and Transparency

ATLA 39, 317–337, 2011

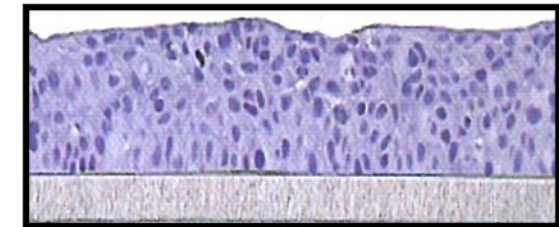
317

Vaginal Irritation Models: The Current Status of Available Alternative and *In Vitro* Tests

Gertrude-Emilia Costin,¹ Hans A. Raabe,¹ Robert Priston,² Eric Evans³ and Rodger D. Curren¹

¹Institute for In Vitro Sciences, Inc. (IIVS), Gaithersburg, MD, USA; ²The Kimberly-Clark Europe Limited, Reigate, Surrey, UK; ³The Kimberly-Clark Corporation, Roswell, GA, USA

Reconstructed human vaginal
epithelium (SkinEthic™ HVE)
from EpiSkin



A431 cells, derived from human
vulva epidermoid carcinoma

Technical Characterization

Preliminary Data on Personal Lubricants Tested with the NAM Intended for Qualification

Flow Chart: RHVE Test Method for Next Steps of Qualification

0- Storage of tissue

- Upon receipt, store the EpiVaginal tissue-containing sealed plate at 20-25°C until use and the remaining components according to the provider's instructions [MatTek, EpiVaginal (Part No. VEC-100) and MTT Assay Kit (Part No. MTT-100)].

1- Evaluation of product interference with MTT assay

- Add 100 μ L product to 1 mL of 1.0 mg/mL MTT.
- Add 100 μ L of sterile, deionized water to 1 mL of 1.0 mg/mL MTT as control.
- Incubate the mixture at standard culture conditions for 1 to 3 hours.
- If the MTT solution turns blue/purple, perform a freeze-killed control experiment (refer to Supplementary Material and Methods).
- If not, continue as described below.

2- Tissue preparation

- Transfer tissues from the agarose package to a 6-well plate containing 0.9 mL Assay Medium per well.
- Incubate tissues at standard culture conditions (humidified incubator at 37 $\pm$ 1°C, 5 $\pm$ 1% CO₂, and 90 $\pm$ 10% relative humidity) for one hour.
- Replace medium with 0.9 mL fresh medium.

3- Treatment

- Apply 100 μ L of product or control to the apical side of the tissue.
 - 3 tissues per product or control to generate 3 biological replicates
 - Positive control: 1% (w/v) Triton X-100 solution
 - Negative control: Untreated tissues
- Incubate tissues at standard culture conditions for the respective exposures.
 - Positive control: 0.5, 1, and 2 hours
 - Negative control and products: 1, 4, and 24 hours
- Remove product and control by extensively rinsing both sides of the tissue culture with CMF-DPBS using a plastic squeeze bottle once the exposure time has been reached.
- Save media from 6-well plate and store at -20 $\pm$ 1°C for potential subsequent cytokine analysis or LDH (to be determined).
- Decant excess CMF-DPBS and blot tissue insert on sterile paper towel.

4- MTT assay

- Add 300 μ L of 1.0 mg/mL MTT solution per well in a 24-well plate.
- Transfer the tissue insert to the 24-well plate.
- Incubate under standard culture conditions for 3 $\pm$ 0.1 hours.
- Blot tissue insert on sterile paper.
- Transfer tissue insert to 24-well plate containing 2.0 mL of isopropanol per well.
- Seal the plate and store at 2-8°C until the last exposure time is harvested.
- Shake the plate for 2-3 hours at room temperature.
- Combine apical and basal solution of each insert and mix.
- Transfer 200 μ L to a 96-well plate and include two wells with 200 μ L isopropanol as blank control.
- Measure optical density (OD) at 570 nm with an appropriate plate reader (for example: Molecular Devices VersaMax).

5- Data analysis

- Calculate the mean OD value of the two blank controls, subtract it from the mean negative control OD value and from the individual product and positive control OD value at each exposure time.
- Calculate the % viability:

$$\% \text{ viability} = \frac{\text{blank corrected OD of positive control or product}}{\text{mean blank corrected OD of negative control}} \times 100$$
 - Note 1: for the % viability of the positive control, use the blank corrected OD value of the negative control at the 1-hour exposure
 - Note 2: for the % viability of the product, use the blank corrected OD value of the negative control at the corresponding exposure (eg. 1, 4 or 24 hours)
- Calculate the mean % viability, its standard deviation (SD), and the ET₅₀ values for the positive controls and the products (see main manuscript).
- Calculate the coefficient of variation (CV).

6- Test acceptance criteria (may require readjustment during the qualification)

- The test is deemed valid if the following four criteria are fulfilled:
 - ET₅₀ value (positive control) is within 2x SD of the mean ET₅₀ value (positive control) established by the testing facility (mean ET₅₀ and SD are updated every 3 months)
 - ET₅₀ value (positive control) > 0.5 hours
 - OD value (negative control) 1-hour exposure $\geq$ 1.0
 - CV (% viability) of all positive and negative controls $\leq$ 20%
- The product ET₅₀ value is deemed valid if the test is deemed valid
 - CV (%viability) of product at 1, 4, and 24 hours exposure will be monitored during qualification as more products are tested.

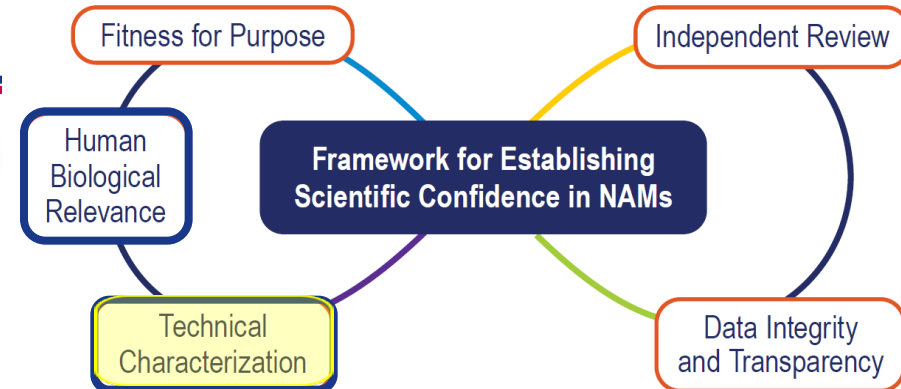
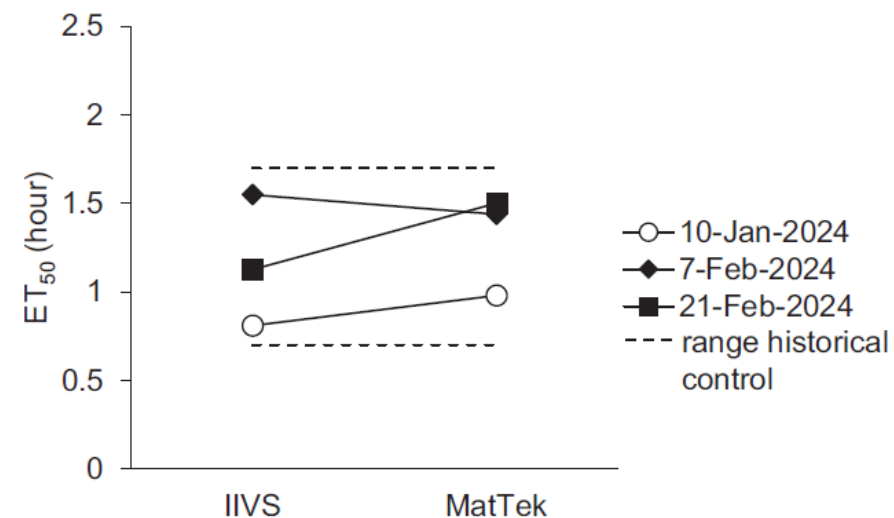
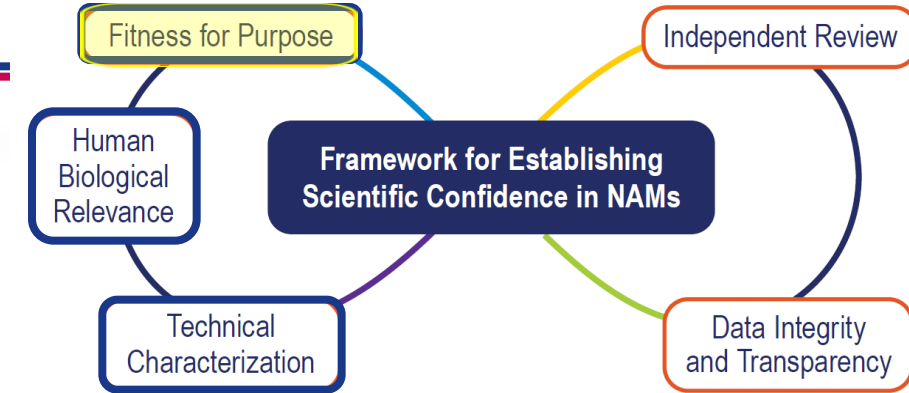


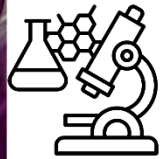
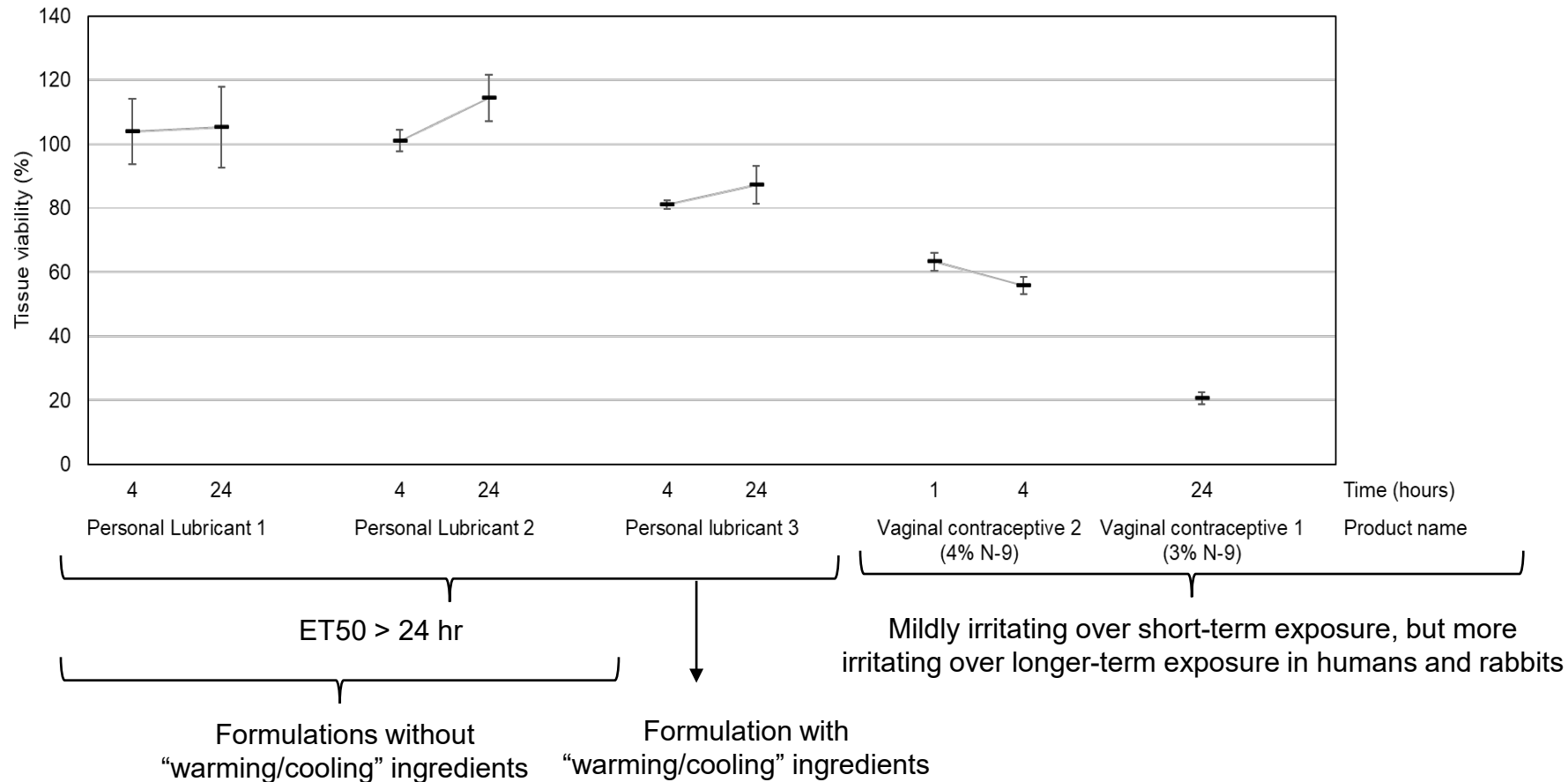
Fig. 4. ET₅₀ values for 1% (w/v) Triton X-100 in the inter-laboratory testing.

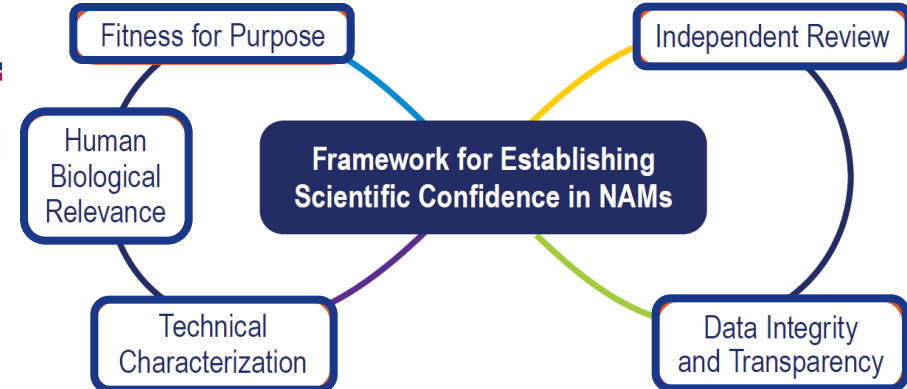
Fit for Purpose

Preliminary Data on Personal Lubricants Tested with the NAM Intended for Qualification



Can rank personal lubricants according to their irritation potential





Toxicology in Vitro 112 (2026) 106198



ELSEVIER

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Toxicology in Vitro

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



Using a reconstructed human vaginal epithelium model to assess irritation:
A proof-of-concept study supporting regulatory qualification of the method
for use with personal lubricants

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Real-life Evaluations

Personal Lubricant Registered as Medical Device



FDA U.S. FOOD & DRUG
ADMINISTRATION

November 21, 2019

Good Clean Love, Inc.
% Steven Chernoff
Vice President
Drug & Device Development Co., Inc.
P.O. Box 3515
Redmont, WA 98073

Re: K150094
Trade/Device Name: Good Clean Love Personal Lubricants Almost Naked
and Natural Cinnamon Vanilla
Regulation Number: 21 CFR 884.5300
Regulation Name: Condom
Regulatory Class: Class II
Product Code: NUC
Dated: September 30, 2015
Received: October 2, 2015

510(k) Premarket Notification – K150094



Good Clean Love

Non-clinical testing:

Testing has established that lubricants met specifications for appearance, odor, pH, viscosity, osmolality, antimicrobial effectiveness, total microbial count, fungal/yeast/mold limits, and absence of pathogenic organisms. Shelf-life has been established at one-year.

Condom compatibility testing following ASTM D7661-10 concluded that the lubricants are compatible with natural rubber latex, polyisoprene, and polyurethane condoms.

Biocompatibility testing for Vaginal Mucosa Irritation (ISO 10993-10:2010), Acute Systemic Toxicity (ISO 10993-11:2006), Maximization Test for Delayed Hypersensitivity (ISO-10993-10:2010), and Cytotoxicity (MatTek EpiVaginal Tissue Model) all had acceptable results.

Conclusion:

The conclusions drawn from the non-clinical tests and predicate comparison demonstrate that the subject device performs as well as the legally marketed device and the Good Clean Love's personal lubricants are substantially equivalent to the cited predicate device for intended use and technological characteristics.

Safety assessment scheme for menstrual cups and application for the evaluation of a menstrual cup comprised of medical grade silicone



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Summary

Background Ensuring menstrual cup safety is paramount, yet a menstrual cup safety assessment scheme is lacking. This paper presents a quadripartite scheme, showing how it can be applied.



eBioMedicine
2022;86: 104339

Published Online 10
November 2022

Assessment of irritation potential

In the *in vitro* EpiVaginal™ assay, ET₅₀ values > 24 h were recorded for all test materials, (1) Tampax Cup in sesame oil; (2) Tampax Cup in saline; (3) the punch of an Always Feminine Wipe; and (4) the liquid expressed from a further wipe. There was some reduction in viability for the EpiVaginal™ tissues treated with the liquid expressed from the wipes (53.5% viability at 16 h, 77.7% viability at 24 h). Hence, the response curve for the liquid indicates some toxicity compared to the punch. This was anticipated given the difference in the liquid volume when using the punch (which includes the wipe and the lotion) vs the liquid (i.e. the lotion alone). From a risk assessment perspective, the former is more indicative of the clinical use situation. Therefore, these results are considered more relevant.

The Quality Triforce Plus



- Quality systems provide a strong base to support confidence in the methodologies.
- Educational activities enhance the speed at which information can be communicated between the corners of the triangle.

Thank You

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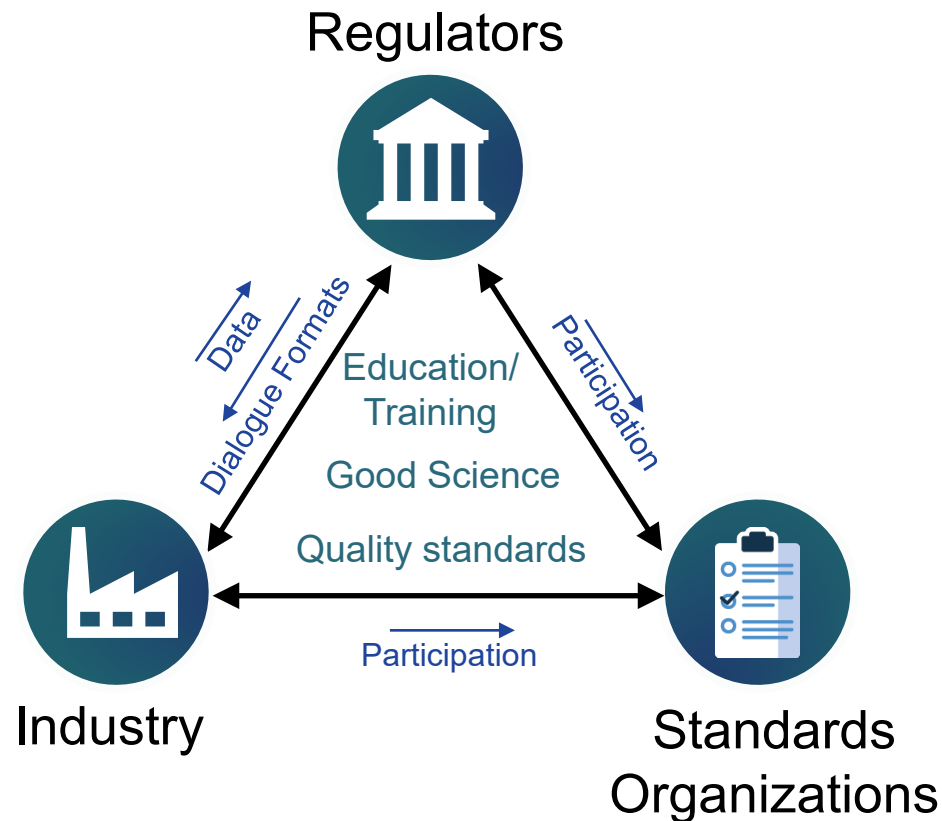
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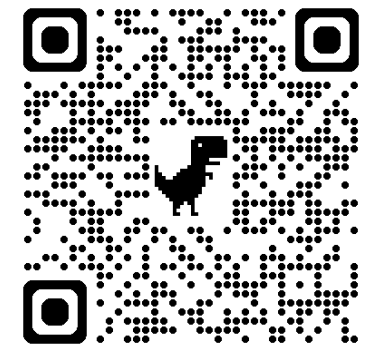
Science
Education &
Outreach

Global adoption of NAMs for medical devices

The “awkward triangle”



Presentations
Literature & Resources

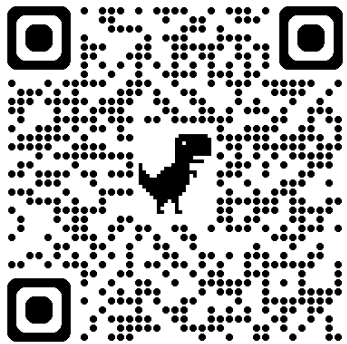


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Panel Discussion

Contact: medicaldevices@thePSCI.eu

Presentations
Literature & Resources



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