HUMANE SOCIETY INTERNATIONAL

Substituting LAL with recombinant technologies. A global perspective

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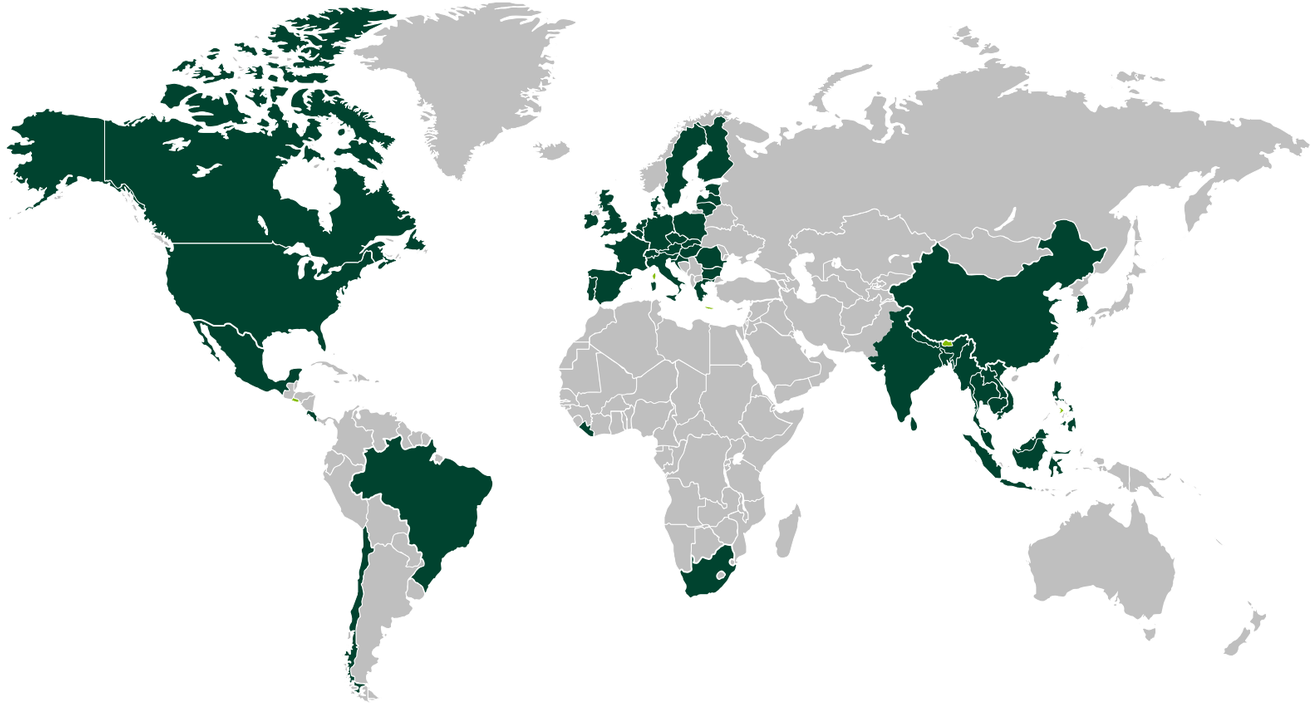
Agenda

- **Introduction of HSI R&T and AFSA and their activities and accomplishments**
- Why HSI is working to promote changes to animal based pyrogenicity?
- Transition to recombinant technologies. Where are we?
- Our strategy for enabling the use and development of these technologies in India

HSI Research & Toxicology program

- HSI's R&T team includes experts in regulatory science, biomedicine, government and corporate relations, advocacy and science communications
- Working cooperatively with industry, regulators, lawmakers, researchers, funding bodies, and other stakeholders to achieve lasting change
- Working for animals and science in more than 50 countries



Countries with R&T staff &/or program activity

HSI's strategic approach

"Building partnerships for progress"

Increase science funding for human-centric, non-animal technologies and predictive models

Build stakeholder capacity and confidence in animal-free safety assessment and human-centric research design

Accelerate regulatory acceptance, global alignment, and mainstream use of animal-free approaches

Promote use of objective tools to evaluate the validity and translational value of models of human biology and disease

Overcome animal reliance bias in publication

Modernize laws and regulations to lay the foundation for a paradigm shift away from reliance on animals for testing and research

AFSA COLLABORATION

The HSI-coordinated Animal-Free Safety Assessment (AFSA) Collaboration works to accelerate global adoption of a modern, species-relevant approach to safety assessment that will better protect people and our planet and hasten the replacement of animal testing.

Cosmetics

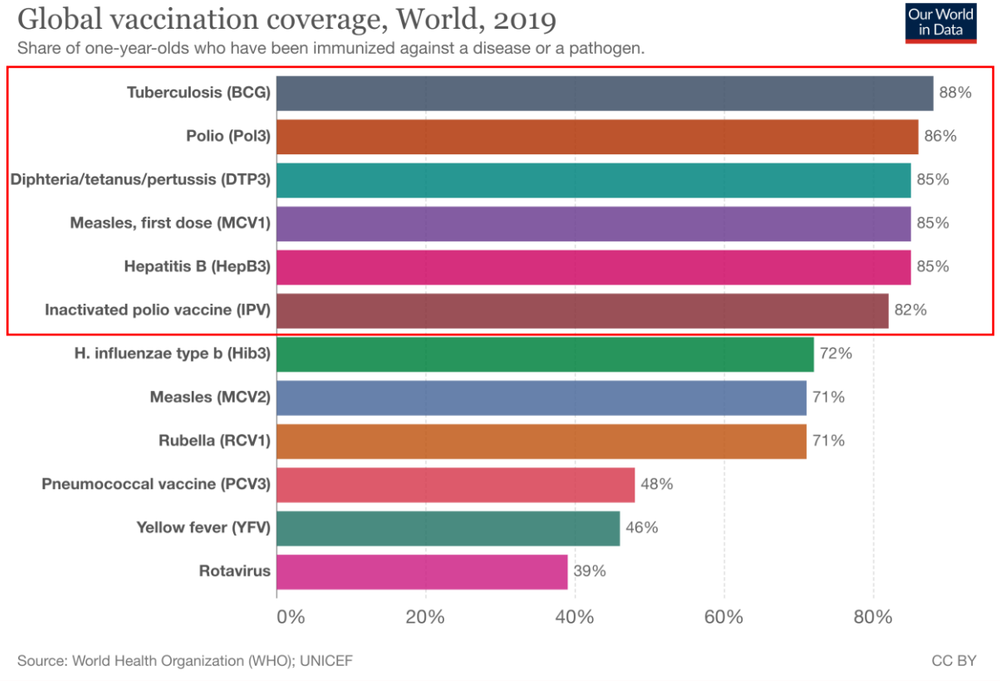
Chemicals

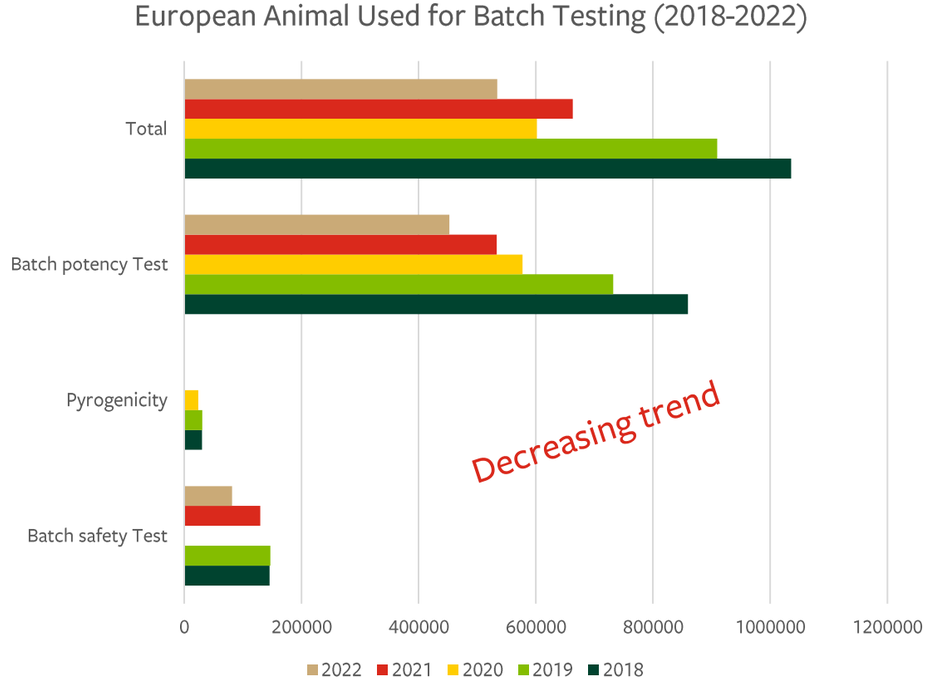
Medicines

Our current AFSA Collaborators

AFSAcollaboration.org

How big is our challenge?





Legacy vaccines (developed decades ago) heavily rely on animal testing for quality control

Over 14 million animals per year used for vaccines worldwide (conservative estimation)

What our collaborations have accomplished

Complete and partial deletion of the abnormal toxicity test for human vaccines

- Brazil (2019)
- India (2021)
- South Korea (2022)
- Indonesia (2022; product-specific waivers after company's request)
- Russia (eased position toward test waiver, deletion and reduction)

Regulatory requirement for the waiver of the animal batch safety tests (veterinary vaccines)

- Brazil (2022)
- India (2024)

- Organized dedicated local and global multi-stakeholder meetings and workshops in both human and veterinary fields
- www.afsacollaboration.org/biologicals/vaccines-regulatory-alignment

Collaborate with global and local stakeholders to promote implementation and acceptance of MAT to replace RPT and recombinant Factor C to replace BET based on LAL

- Brazil (2022): streaming event dedicated to MAT; established a local WG on MAT implementation
- New AFSA partner: bioMèrieux. Collaborate to promote rFC adoption in India, South Korea, China, Brazil

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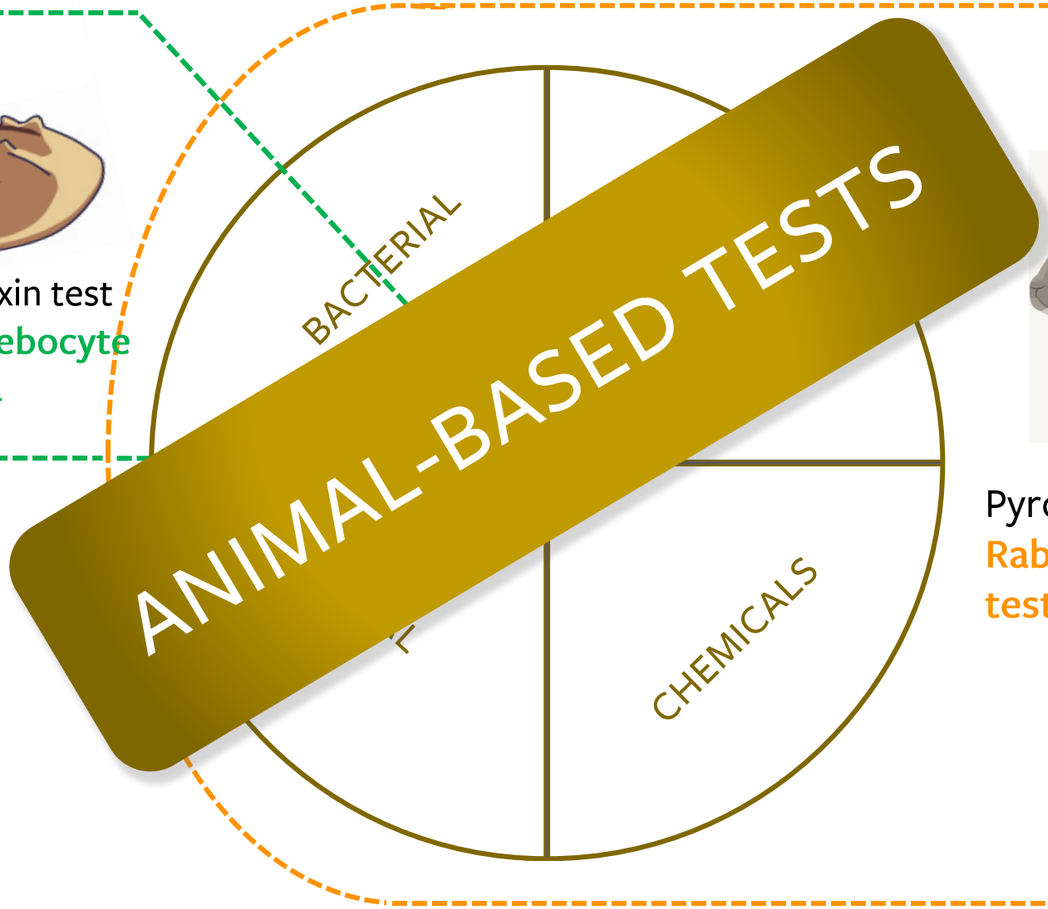
Animal-based Methods For Pyrogen Testing

Bacterial endotoxin test by **Limulus amoebocyte lysate test - LAL**



Pyrogen testing by **Rabbit pyrogen test - RPT**

Considerations for shifting from animal-based methods to alternative assays

Quality and consistency

recombinant methods offer a more precise, sensitive, and reproducible method of detecting endotoxin

Global supply chain uniformity

Horseshoe crab-derived reagents are a pool of various bled animals with different sexes, age, physical conditions, locations and genetic composition, etc. Recombinantly produced reagents are produced repeatedly from the same stock of genetically modified single-celled organisms in a bioreactor

Supply chain reliability

Horseshoe crabs are present in certain geographic locations. Concerns have arisen regarding access of this raw material to pharma companies that are present outside of their endemic regions due to changing geopolitical landscape

Environmental sustainability

Given the unpredictable advance of climate change, there is growing evidence of changing temperatures and sea levels affecting natural supply sources

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Transition to recombinant technologies. Where are we?

Methodologies readiness	▪ Recombinant technologies are validated and available in major markets ▪ New methods are considered equivalent if not superior to the traditional animal-based LAL
Regulatory Acceptance and global harmonization	▪ More and more countries are including recombinant technologies in their requirements (see next slide) ▪ Work is still needed to get more countries onboard and have aligned requirements
Implementation of the method	▪ Biopharmaceutical companies globally and locally are committing to transition from LAL to recombinant BET (e.g. PSCI link: https://pscinitiative.org/bulletin?bulletin=629) ▪ Acknowldege that transition requires planning and investment and difficulties might be solved due to country, regional company specific situations

rfc Regulatory Update 2023

US Pharmacopeia

Guidance for Industry, Pyrogen and Endotoxins Testing: Q&A

MAPP 5310.7

Supports and accepts the use of rFC to replace LAL

Harmonised
USP <85> Bacterial Endotoxins Test

USP <1085.1> Use of Recombinant Reagents in Bacterial Endotoxins Test on hold (Jun 2021)

USP <1223> Validation of Alternative Microbiological Methods

USP General Chapter <86>) Bacterial Endotoxin testing using Recombinant

Alternative

EU Pharmacopeia

Harmonised
Ph. Eur. 2.6.14 Bacterial Endotoxins

Ph. Eur. 2.6.32 Test for Bacterial Endotoxins with Recombinant Factor C (rFC)

Compendial 2021

Ph. Eur. 5.1.10 Guidelines for using the test for bacterial endotoxins

Inclusion of rFC in the monographs:

- Water, purified (0008)
- Water for injections (0169)
- Gene Therapy Medicinal Products for Human Use

EAEU Pharmacopoeia

To add a chapter on Test for Bacterial Endotoxins with Recombinant Factor C (rFC) based on Ph. Eur. 2.6.32

Compendial 2023

Korean Pharmacopoeia

2022 completed a **comparison study rFC vs. LAL and confirmed to become part of the KP in 2023**

Compendial 2023

CH Pharmacopeia

ChP 1143 Bacterial Endotoxins Test

ChP 9251 Guideline for BET Application (introduction of the rFC)

Alternative 2020

JP Pharmacopeia

Harmonised
JP 4.01 Bacterial Endotoxins Test

HP G4-4-180 Bacterial Endotoxins Test & Alternative Methods using Recombinant Protein-reagents for Endotoxin Assay

Alternative 2021

Indian Pharmacopeia

IP 2.2.3 Bacterial Endotoxins

Guidelines on the BET Introduction of Alternate Test Methods

Alternative 2023

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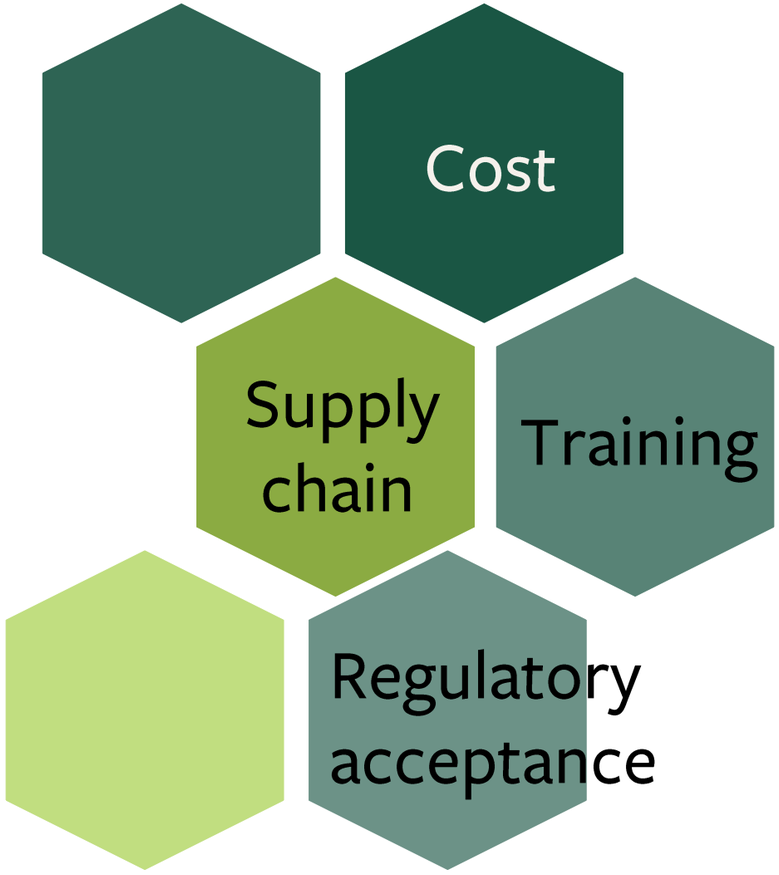
Our approach

Our Strategy in India and other countries



Stakeholder engagement: identify and engage all the relevant stakeholders in India (biopharmaceutical companies, associations, suppliers, CROs, IPC, CDSCO, academia, etc.)

Cost analysis: To assess using stakeholder dialogue if cost is an impeding factor in this shift.

Supply chain: Assess if availability of kits, reagents, raw material etc. is a significant factor. If yes, identify and enable possible solutions.

Regulatory status: Assess the response of regulators and what is required for acceptance and validation?

Training: Assess if the stakeholders sufficiently aware and trained to use these methods

Enabling the use and development of these methods in India

- Support stakeholders (biopharmaceuticals and regulators) to familiarize with the technology
- Facilitate multistakeholder dialogue and sharing experience
- Encourage biopharmaceutical-regulators early dialogue on process and methods change

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Thank you !

We do look forward to working with you - https://www.afsacollaboration.org/biologicals/

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