Regulatory and Industrial Acceptance of Non-animal Pyrogen Test Methods in India: Challenges and Opportunities

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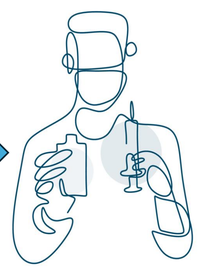
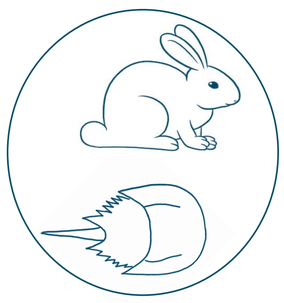
Problem Statement

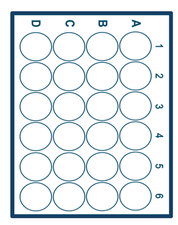
How best to shift pyrogen testing…



from traditional animal tests…



to the most human-relevant methods available?



PETA India is working with regulators, stakeholder companies, policymakers, and researchers to increase the adoption of non-animal pyrogen test methods

Why is this transition needed?

Detecting contamination by fever-causing substances (pyrogens) is an integral part of safety testing for many medical products. Historically, pyrogen tests have used animals, including the Rabbit Pyrogen Test (RPT) and the horseshoe crab-blood based Limulus Amoebocyte Lysate (LAL) test, also called the Bacterial Endotoxin Test (BET). These tests have scientific issues that pose problems in light of increasing complexity in drugs and medical devices, and their production processes.

Non-animal methods are available that can replace the RPT and the BET/LAL. These methods, the recombinant Factor C (rFC) assay and the Monocyte Activation Test (MAT), still require product-specific evaluation to varying degrees as indicated in an increasing number of regulatory standards and other guidance.

There is no formal process that ensures regulatory testing requirements modernize as quickly as new, reliable and human-relevant testing approaches are developed. As a result, PETA India is working to navigate the path to regulatory acceptance of the non-animal pyrogen tests in India.

2024 European Pharmacopoeia: Announces that 57 revised pharmaceutical monographs from which the RPT has been deleted, together with a new general chapter with guidance on non-animal pyrogen testing, will become official 1 July 2025

2024 US Pharmacopeia: Approves new chapter permitting the use of rFC that will become official in May 2025

2018 Eli Lilly's Emgality™ (galcanezumab), the first drug approved by the U.S. FDA that uses rFC as its batch release pyrogen test

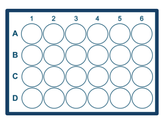
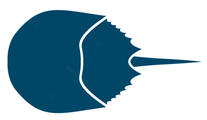
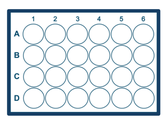
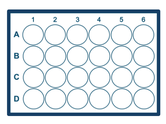
2018 Indian Pharmacopoeia: MAT added as a general chapter

2017 ISO: When evaluating systemic toxicity of medical devices, ISO 10993-11:2017 does not recommend using the RPT for new products, although chemical entities with unknown pyrogenic potential still need to be evaluated for material mediated pyrogens (MMPs)

2016 Japanese Pharmacopoeia: MAT permitted if it can be demonstrated to provide improved accuracy and precision

2009 European Pharmacopoeia: MAT added as general chapter 2.6.30

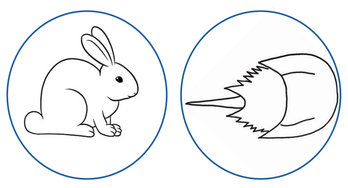
Pyrogen testing methods

Test Type	Detection Method	Limit of Detection	Pyrogens Detected
 Rabbit Pyrogen Test	***In vivo***: Measure rise in body temperature after injection of a drug	0.5 EU/mL	Bacterial endotoxin and non-endotoxin pyrogens
 Monocyte Activation Test	***In vitro***: Measure cytokines released by monocytes from human blood	0.02 – 0.004 EU/mL	
 Limulus Amebocyte Lysate Test	***In vivo***: Measure initiation of clotting cascade by horseshoe crab blood amebocyte	0.005 EU/mL	Gram-negative bacterial endotoxin
 Recombinant Factor C Test	***In vitro***: Recombinant alternative to LAL based on factor C	0.005 EU/mL	
 Recombinant Cascade Reagent	***In vitro***: Recombinant alternative to LAL based on factors C and B, and clotting agents	0.001 EU/mL	

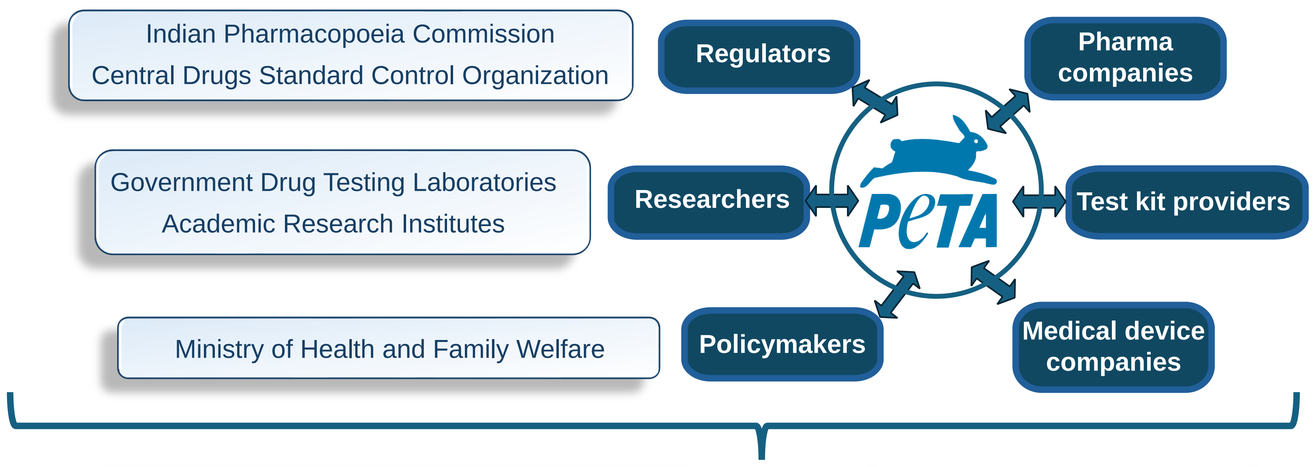
Current status in India

The RPT and the LAL/BET are referenced in the majority of Indian Pharmacopoeia (IP) monographs.

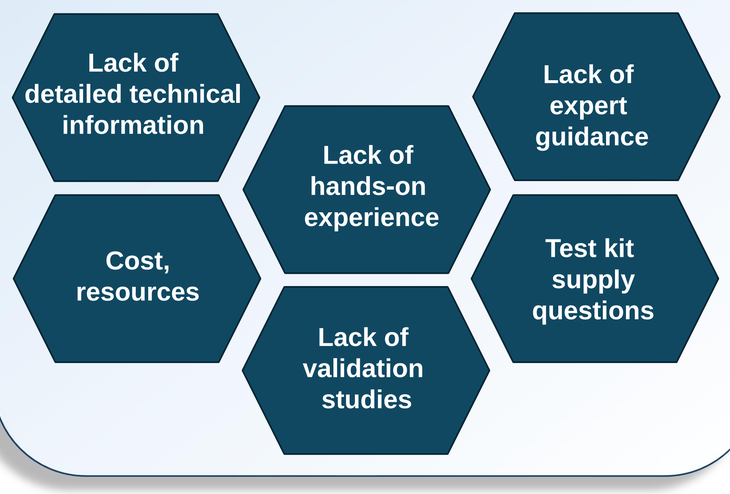
The IP's MAT general chapter was published in 2018, but the RPT is still routinely used in pharmaceutical and medical device testing.



Lessons learned



Shared perspective on challenges



Consensus-building next steps

- Coordinated discussion among stakeholders to prioritize which challenges need to be addressed first
- Hands-on training and technical support requirements of stakeholders
- Collaboration on targeted validation studies
- Inclusion of rFC and MAT in IP product monographs

- ❑ The primary objective of PETA India's initiative is to collaborate with regulators, policymakers, and stakeholders to advance and implement non-animal pyrogen testing methods in alignment with global trends and the state-of-the-science. By fostering partnerships with these stakeholders, PETA India facilitates the exchange of knowledge and accelerates the adoption of innovative technologies by **building consensus on the most appropriate and feasible steps** toward this objective.
- ❑ These stakeholder collaborations emphasize the necessity of **involving all relevant parties** in the planning process. The process includes discussions with companies that generate pyrogen test kits, the companies that purchase and use these kits, as well as the regulators who must be comfortable receiving, interpreting, and making decisions using new sources of data. It also extends to researchers outside the regulatory infrastructure who are often consulted for their technical expertise when regulators and medical product manufacturers are deciding whether the necessary infrastructure exists before committing resources to adopting new approaches in their testing and data analysis routines.
- ❑ Voices from broader scientific and policy sectors have helped identify **a common set of challenges** that all parties agree must be addressed before non-animal pyrogen testing can be routinely used and accepted for regulatory purposes in India. With this in mind, PETA India is coordinating opportunities for these stakeholders to inform a prioritized set of strategic goals to address these challenges in a way that is relevant to, and feasible for, these stakeholders.
- ❑ PETA India's efforts are also leading to much needed opportunities for stakeholders to gain hands-on experience with non-animal pyrogen tests alongside technical experts who can assist with the inherent challenges of integrating new techniques into an organization's repertoire. **Further meetings to organize this process are being held**, including a December 2024 planning and discussion meeting.

References:

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