Using the Monocyte Activation Test for Medical Devices

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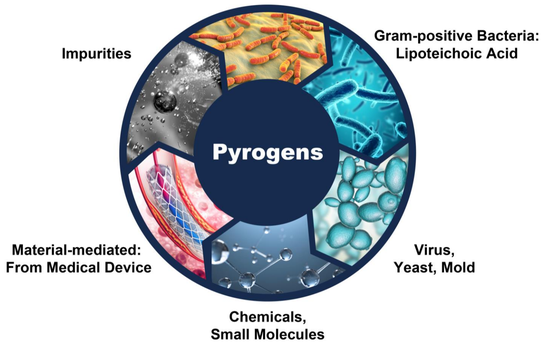
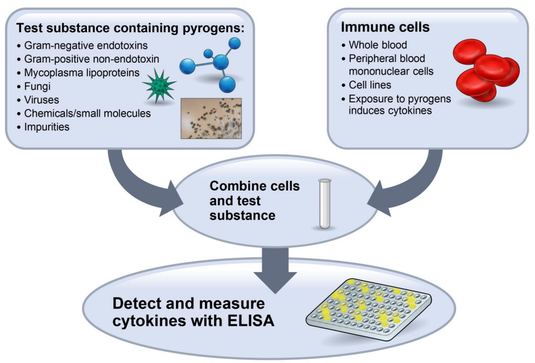
Pyrogen Testing for Medical Devices

- A pyrogen is any substance that induces fever.
- Most pyrogens are biological substances derived from bacteria, fungi, and viruses. Chemicals that act as material-mediated pyrogens, while less common, may also be present.



- Medical device products for implantation must meet pyrogen limit specifications before they are marketed.
- Monocyte activation tests (MATs) are human cell-based tests to detect and quantify pyrogens. MATs use an ELISA assay to measure cytokine release from treated blood cells.

Principle of the Monocyte Activation Test



- MATs are widely available but rarely used in place of animal-based pyrogen tests for biocompatibility assessment of medical devices.
- The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the PETA International Science Consortium Ltd. (PISC) convened a September 2018 workshop at the National Institutes of Health to discuss necessary steps towards implementation of MAT use in medical device testing.

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Workshop Speakers and Presentations

Speaker	Affiliation	Presentation
Thomas Hartung	Johns Hopkins Center for Alternatives to Animal Testing	Introduction and overview: Monocyte activation tests
Molly Ghosh	FDA Center for Devices and Radiological Health – Biocompatibility Standards Task Group	The FDA MDDT program and considerations for MAT testing of medical devices
Anita Sawyer	International Organization for Standardization Technical Committee 194, Biological and Clinical Evaluation of Medical Devices	Material-mediated pyrogenicity and ISO TC 194 standards
Radhakrishna Tirumalai	United States Pharmacopoeia	Alternate pyrogen tests
Kelly Coleman	Medtronic	Material-mediated pyrogens in medical devices

All presentation slides can be accessed at https://www.piscltd.org.uk/medical-device-pyrogen/.

Potential Sources of Pyrogens in Medical Devices

Bacterial Endotoxins

- Assessed as part of sterility assessment
- Standard test: limulus amoebocyte lysate test, also known as the bacterial endotoxin test (BET)

Potentially Pyrogenic Chemicals

- Include manufacturing residuals that may leach out from devices during clinical use, resulting in material-mediated pyrogenicity (MMP)
- Assessed as part of biocompatibility assessment
- Standard test: rabbit pyrogen test (RPT) per USP <151> (USP 2018)
  - Detects both endotoxin and non-endotoxin-mediated pyrogenic response
  - Gives a yes (pyrogenic) / no (not pyrogenic) answer
  - Requires a large number of test samples

Considerations for Qualification of an Alternative to the RPT

- Is the proposed test going to replace both BET and RPT?
  - If so, is the test qualified for detection of both endotoxin and non-endotoxin pyrogens?
  - Does a test qualified for detection of non-endotoxin pyrogens detect both MMPs and microbial components other than endotoxin?
- How does the endpoint measured in the test relate to the complex process of fever response in humans?
- Are there any chemicals or device designs known to be incompatible with the test system?
- What has been done to verify that articles or extracts to be tested will not interfere with the cell system or with the cytokine-specific ELISA used in the test?
- Can this test be qualified for varying regulatory "endotoxin units (EU) per device" limits? Examples include:
  - Devices in direct or indirect contact with cardiovascular system and lymphatic system: 20 EU/device
  - Devices in contact with cerebrospinal fluid: 2.15 EU/device
  - Intraocular lenses: ≤0.2 EU/device
- What are the appropriate positive controls for demonstrating the ability to detect non-endotoxin pyrogens?
- What qualification data already exist for the proposed test, and what data gaps still need to be filled?

Comparison of the RPT and MAT

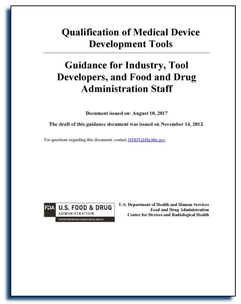
RPT	MAT
Requires the use of rabbits	Uses human whole blood and human cell lines
Well-accepted by regulatory agencies for MMP detection	No regulatory acceptance for MMP on medical devices
Fails to detect some human pyrogens	More false positives than RPT, but detects all known human pyrogens tested to date
No internal positive and negative controls	Potential for internal positive and negative controls
Pass/fail qualitative assessment	Quantitative assessment

International Evaluation and Acceptance of the MAT

- In 2006 and 2008, respectively, the European Center for the Validation of Alternative Methods and the Interagency Coordinating Committee on the Validation of Alternative Methods endorsed the MAT for identifying Gram-negative endotoxins.
- In 2009, the U.S. Food and Drug Administration (FDA) acknowledged that the MAT may be used after product-specific validation, and subsequently published guidance that possible use of the MAT if product-specific validation is provided for FDA-regulated products such as medical devices (FDA 2009, 2012).
- In 2010, the MAT was integrated into general chapter 2.6.30 ("Monocyte Activation Test") in the European Pharmacopoeia and described as a full replacement for the RPT following product-specific validation (EDQM 2010).
- The U.S. Pharmacopeia General Chapter <151> ("Pyrogens") allows use of a "validated, equivalent *in vitro* pyrogen or bacterial endotoxin test" in place of the RPT (USP 2018).
- ISO 10993-1:2009 gives preference to *in vitro* models when they yield equally relevant information (ISO 2009).

FDA Medical Device Development Tool Program

- The FDA's Medical Device Development Tools (MDDT) program is a way for FDA to qualify tools such as pyrogen tests that medical device sponsors use in the development and evaluation of medical devices.
- An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device.
  - An MDDT is scientifically validated and qualified for a specific context of use.
  - "Context of use" describes the way an MDDT should be used, its purpose in device evaluation and/or regulatory submission, and the specific output/measure expected from the tool.


Qualification of Medical Device Development Tools

Guidance for Industry, Tool Developers, and Food and Drug Administration Staff

Document issued on: August 10, 2017

The draft of this guidance document was issued on November 14, 2013.

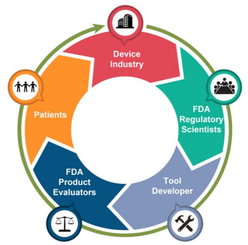
For questions regarding this document, contact MDDT@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health

- "Qualification" represents a conclusion by the FDA that an MDDT has a specific application in medical device development and regulatory review within the described context of use.
  - Successful qualification of an MDDT indicates that FDA Center for Devices and Radiological Health (CDRH) reviewers may accept results from the test in a regulatory submission within the qualified context of use without the need to otherwise reconfirm the suitability and utility of the test.
- The workshop participants recommended that the FDA MDDT program be the primary venue through which efforts to demonstrate the usefulness of the MAT as a replacement for the RPT and/or BET in medical device regulatory submissions be focused.

MDDT Program: Benefit of Qualifying Tests



- Fosters innovation
- Encourages collaboration
- Reduces resource expenditure
- Qualified MDDT applied in multiple device submissions
- Efficiency in CDRH regulatory review resources
- Minimizes uncertainty in regulatory review process
- Reduces regulatory burden

The MDDT program engages all relevant stakeholders in the discovery and development of new tools for medical device testing.

Inquiries for additional information on MDDT email: MDDT@fda.hhs.gov or https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt

Next Steps

- Workshop attendees agreed that next steps should include MDDT proposal development for implantation of the MAT that includes:
  - Proposed context of use
  - Description of the MAT test methods
  - Overview of the proposed evidence plan that will be used to qualify the MAT
  - Timeline
- NICEATM and PISC will coordinate with companies and CDRH to facilitate MDDT development.
- Training and education on the MAT is a critical activity to facilitate its adoption.
  - USP will present a workshop on **June 10-11, 2019**, in Rockville, Maryland, on the "Future of Endotoxins and Pyrogen Testing: Standards and Procedures." Information on the workshop is available at http://www.usp.org/events-training/workshops/future-of-endotoxins-and-pyrogen-testing

References

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International Organization for Standardization (ISO). 2009. "ISO 10993-1: Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process.

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Acknowledgements

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