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 devices 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.
• 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.
## Workshop Speakers and Presentations

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

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<th>RPT</th>
<th>MAT</th>
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<td>Requires the use of rabbits</td>
<td>Uses human whole blood and human cell lines</td>
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<tr>
<td>Well-accepted by regulatory agencies for MMP detection</td>
<td>No regulatory acceptance for MMP on medical devices</td>
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<tr>
<td>Fails to detect some human pyrogens</td>
<td>More false positives than RPT, but detects all known human pyrogens tested to date</td>
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<tr>
<td>No internal positive and negative controls</td>
<td>Potential for internal positive and negative controls</td>
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<td>Pass/fail qualitative assessment</td>
<td>Quantitative assessment</td>
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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 included 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. Pharmacopoeia General Chapter <151> (“Pyrogens”) allows use of a “validated, equivalent in vitro pyrogen or bacterial endotoxin test” in place of the RPT (USP 2018).
FDA Medical Device Development Tool Program

- The FDA's Medical Device Development Tools (MDDT) program is a way for the 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” 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 Tools

- 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 see https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt
Next Steps

- Workshop attendees agreed that next steps should include MDDT proposal development for implementation 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.

References


United States Pharmacopeia. 2018. "General Chapter <151> ("Pyrogens")." from [http://www.pharmacopeia.cn/v29240/usp29nf24s0_c151.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_c151.html)
Acknowledgements

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