**Using the Monocyte Activation Test for Medical Devices**

D Allen¹, A Clippinger², S Morefield¹, W Casey¹, C Ghosh³, J Goode⁴, J Brown²

¹ILS, RTP, NC, USA; ²PISC, London, UK; ³NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA; ⁴FDA/CDRH, College Park, MD, USA

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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.

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**Workshop Speakers and Presentations**

- **Speaker**
  - Thomas Hartung: Johns Hopkins Center for Alternatives in Animal Testing
- **Affiliation**
  - Introduction and overview: Monocyte activation tests

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**Comparison of the RPT and MAT**

- **RPT**
  - Requires the use of rabbits
  - Uses human whole blood and human cell lines
- **MAT**
  - Well-accepted regulatory agencies for MAT and RPT
  - No regulatory acceptance for MAT for medical device testing
  - Fails to detect some human pyrogens
  - More false positives than RPT, but detects all human pyrogens tested to date
  - No internal positive and negative controls
  - Potential for internal positive and negative controls
  - Failure: qualitative assessment
  - Quantitative assessment

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**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

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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 not provided for FDA-regulated products such as medical devices (FDA 2009, 2012).
- In 2010, the U.S. FDA integrated into general chapter 2,1.30 (“Monocyte Activation Test”) in the U.S. Pharmacopeia and described it as a full replacement for the RPT (following product-specific validation) (USP 2010).
- The U.S. Pharmacopeia General Chapter 1515 (“Pyrogens”) allows use of a “validated, equivalent in vitro pyrogen or bacterial endotoxin test” in place of the RPT (USP 2012).
- ISO 10993-1:2016 gives preference to pyrogen or bacterial endotoxin tests over the MAT.

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**Considerations for Qualification of an Alternative to the RPT**

- **Is the proposed test going to replace both the RPT and MAT?**
  - If so, is the test qualified for detection of both endotoxin and non-endotoxin pyrogens?
- **Does a test qualify for detection of non-endotoxin pyrogens?**
  - Are there any chemicals or device designs known to be incompatible with the test system?
  - Has what been done to verify that articles or extracts to be tested will not interfere with the test system or add to the cytokine-specific ELISA used in the test?
- **Can the 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: 25 EU/device
    - Devices in contact with cerebrospinal fluid: 2.5 EU/device
    - Intravenous leukemias: 45 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?

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**FDA Medical Device Development Tool Program**

- The FDA’s Medical Device Development Tool Program (MDDT) program is a way for FDA Center for Devices and Radiological Health reviewers to accept pyrogen or bacterial endotoxin tests “in place of the traditional ‘ validated, equivalent'” at the time of the RPT
- A test is scientifically validated and qualified for a specific context of use.
- **Context of use** describes the way and where the test will be used, in particular in device evaluation and/or regulatory submission, and the specific context of use.
- **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 negative endotoxin test results from 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 and/or RPT in medical device regulatory submittals be focused.

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**References**


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