THE MONOCYTE ACTIVATION TEST FOR ASSESSING PYROGENICITY

The monocyte activation test (MAT) is a replacement for the rabbit pyrogen test (RPT) and the bacterial endotoxins test (BET)/limulus amoebocyte lysate (LAL) test. The MAT measures cytokine release from monocytes when human blood is exposed to a test substance. Cytokines released in the activation process are quantified by the enzyme-linked immunosorbent assay (ELISA).

ADVANTAGES OF THE MAT

- Based on the human fever response, the MAT provides a more relevant prediction of pyrogenic activity than the RPT or BET/LAL.
- It can detect endotoxin and non-endotoxin pyrogens and is applicable to a greater variety of products than the RPT or BET/LAL (e.g. certain drugs and herbal formulations; see Hartung T. 2015. *ALTEX*. 32(2):79-100).
- It has a lower limit of detection and is more accurate as well as more cost-effective and efficient than the RPT.
- Five variants of the MAT have been standardised and validated.
- Protocols using cryopreserved monocytes derived from individual donors are available (Koryakina A. *et al.* 2014. *J Immunol Methods*. 405:181-191).

SELECT PUBLICATIONS

- Borton L, Coleman K. 2018. Material-mediated pyrogens in medical devices: Applicability of the *in vitro* Monocyte Activation Test. *ALTEX*. 35(4):453-463.
- da Silva C *et al.* 2016. Applicability of the monocyte activation test (MAT) for hyperimmune sera in the routine of the quality control laboratory: comparison with the rabbit pyrogen test (RPT). *Toxicol In Vitro*. 32:70-75.
- Stang K *et al.* 2014. Highly sensitive pyrogen detection on medical devices by the monocyte activation test. *J Mater Sci Mater Med*. 25(4):1065-1075.
- Hasiwa N *et al.* 2013. Evidence for the detection of non-endotoxin pyrogens by the whole blood monocyte activation test. *ALTEX*. 30(2):169-208.
- Hennig U. 2013. Implementing the *in vitro* pyrogen test: one more step toward replacing animal experimentation. *Altern Lab Anim*. 41(5):P58-60.

GUIDANCE

- The ***European Pharmacopoeia*** general method 2.6.30 Monocyte-activation test allows the MAT to serve as a full replacement for the RPT after product-specific validation.
- The **International Conference on Harmonisation** "recommends that the analytical procedures described in the official pharmacopoeial texts, *European Pharmacopoeia* (Ph. Eur.): 2.6.14. Bacterial Endotoxins, *Japanese Pharmacopoeia* (JP): 4.01 Bacterial Endotoxins Test, and *United States Pharmacopeia* (USP) General Chapter <85> Bacterial Endotoxins Test, can be used as interchangeable in the ICH regions subject to the [specific] conditions". See the **US FDA's CDER and CBER**, "Guidance for Industry: Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions, Annex 14, Bacterial Endotoxins Test General".
- ***US Pharmacopeia*** general chapter <151>, "Pyrogen Test", allows use of a "validated, equivalent *in vitro* pyrogen or bacterial endotoxin test" in place of the *in vivo* RPT.
- The **US FDA's** "Guidance for Industry: Pyrogen and Endotoxins Testing Questions and Answers" (2012) states that alternatives, specifically the MAT, may be used after product-specific validation for biological products, drugs, and devices, even when *US Pharmacopoeia* monographs require the RPT. The FDA encourages companies to contact the agency to discuss alternative test methods (e.g. in "Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants and FDA's guidance on its Pre-Submission Program and Meetings").
- The MAT has been accepted into the US FDA's Medical Device Development Tools (MDDT) programme and is undergoing review to qualify as a standalone release test for medical devices that can replace the use of the RPT and BET/LAL when satisfying biocompatibility and sterility testing requirements.
- **ISO 10993-1:2009** "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process" gives preference to *in vitro* models when they yield equally relevant information.
- The **US FDA's CDRH** guidance (2016) states that the CDRH accepts validated methods equivalent to the RPT.
- In 2006 and 2007, respectively, ECVAM and ICCVAM endorsed the MAT for identifying Gram-negative endotoxins and recognised its capacity to detect a wider range of pyrogens. Considerable research has since supported its wider application.

Companies offering MAT kits or services include MAT Research, PyroDex, MilliporeSigma, and Microcoat Biotechnologie GmbH.

For more information, please see PISCLtd.org.uk/medical-device-pyrogen.

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