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EUROPEAN NEWS

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Pyrogens, alternative methods: monocyte activation test

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The Monocyte Activation Test (MAT), also known as the Human Cell-Based Pyrogen Test (HCPT) in ISO/TR 21582, is an *in vitro* assay based on the response of human cells to pyrogens that may be bacterial endotoxins or non-endotoxin pyrogens. Specifically, the test utilises the release of cytokines from monocytes or monocytic cell lines that indicate the presence of pyrogenic contaminants.

This technique offers various advantages over the more traditional Bacterial Endotoxin Test (BET) and Rabbit Pyrogen Test (RPT). Indeed, BET is limited by the fact that it can only detect endotoxins while RPT carries several drawbacks such as poor robustness, the potential for differing immune responses between rabbits and humans, the inability to test various products including chemotherapeutics, immunosuppressive agents, and human cellular preparations. Moreover, both methods present ethical problems related to animal testing.

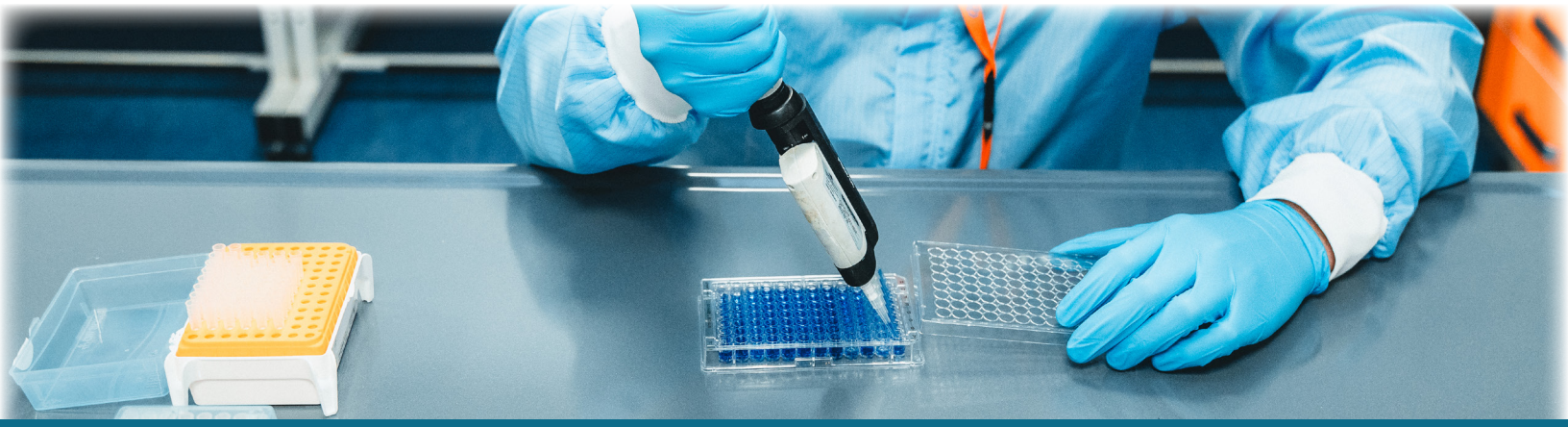
During the MAT, the sample is tested in appropriate dilutions, both with and without added endotoxin. The response, in terms of cytokine production, is compared to an endotoxin standard curve. Non-endotoxin pyrogens may be run in parallel, and the choice of the appropriate molecule should be based on the manufacturing process and microbiological data.

Although MAT is widely accepted in Europe for pharmaceutical products, this technique is considered by the FDA as an alternative method and its validation is therefore required.

In the medical device field, MAT is specifically discussed in ISO/TR 21582. This standard addresses the issue of material-mediated pyrogens (MMP) and defines the RPT as the only test capable of detecting such materials. Consequently, medical devices must still be tested for MMP to gain regulatory approval.

However, this topic is currently being debated, as MMPs are rarely found in medical devices, and their role and mechanism remain largely unclear.

Further insights into MMPs may be provided by the updated version of ISO 10993-1, which is currently in the drafting phase.



Non conformities: how to answer them?

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Medical device manufacturers face diverse challenges in complying with the European Union Medical Devices Regulation (EU MDR 2017/745). The MDR aims to ensure high standards of quality, safety, and performance for medical devices, thereby safeguarding the health of patients and users. To access the European market, manufacturers must obtain the CE mark by fully complying with the regulation.

One primary challenge is navigating the evolving regulatory landscape, which includes meeting stringent product safety requirements, adhering to technical specifications, and maintaining a robust quality management system with extensive documentation. Transitioning from previous directives to the new MDR framework has proven particularly challenging: manufacturers encounter a lot of difficulties in ensuring complete submissions and maintaining updated certifications

Incomplete documentation is a significant reason for submission rejections. For example, preclinical data must comply with ISO 10993-1, which mandates thorough biological evaluations. If degradation products are identified, a detailed toxicological risk assessment must be provided. Clinical documentation also presents challenges, as manufacturers must demonstrate device safety and performance across various patient populations with recent, comprehensive data.

Additionally, the MDR mandates the appointment of a “Person Responsible for Regulatory Compliance” (PRRC), who must have appropriate qualifications. Their role must be clearly defined in organisational documentation; failure to do so can hinder regulatory compliance.

It is of primary importance that MDR requirements and Medical Device Coordination Group guidelines are understood. Common pitfalls include insufficient preclinical, clinical, and quality documentation. Continuous training and regular updates are essential for manufacturers to remain compliant with evolving regulatory standards, and a proactive approach is crucial to navigating the complexities of the MDR and successfully bringing medical devices to market.

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Special Hemocompatibility Testing: Considerations for testing transfusion equipment sets according to ISO 1135-4/-5

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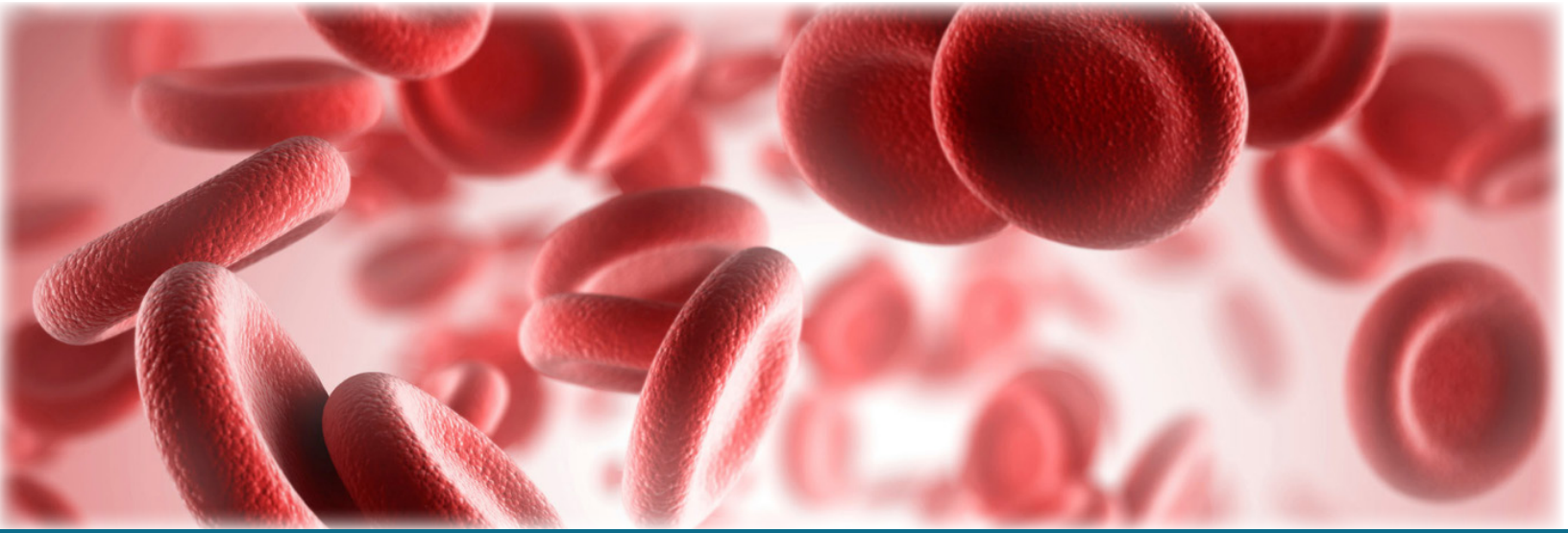
The ISO 1135 guidelines provide a comprehensive framework for the hemocompatibility analysis of transfusion equipment used in medical settings. These standards ensure that the equipment is safe and effective for blood transfusions, minimising the risk of adverse reactions in patients. ISO 1135-4 focuses on transfusion equipment that operates with gravity feed, while ISO 1135-5 addresses transfusion equipment used with pressure infusion apparatus.

When evaluating the hemocompatibility of transfusion equipment in accordance with ISO 1135-4 and ISO 1135-5, two critical assessment parameters are considered: depletion of blood components and damage to blood components.

Depletion of Blood Components: A primary concern during transfusion is the potential depletion of essential blood components. This parameter evaluates how the transfusion equipment impacts the levels of various blood components, such as red blood cells, platelets, and plasma proteins. The goal is to ensure that the equipment does not excessively deplete these components, which are vital for the patient's health and recovery.

Damage to Blood Components: Another crucial aspect of hemocompatibility testing is assessing any potential damage to blood cells and other components caused by the transfusion equipment. This includes evaluating the mechanical stress and shear forces exerted on blood cells and on plasma proteins as they pass through the equipment. Damage to red blood cells, for instance, can lead to hemolysis, potentially causing serious complications. Similarly, damage to platelets and plasma proteins can impair their function, leading to issues with clotting.

The testing process should simulate real-world conditions to observe and measure any adverse effects on blood components. It is therefore recommended to select parameters such as VTBI (Volume to be Infused), flow rates, etc. that closely mimic clinical settings.



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Usability techniques for compliance: the use of Annex C of IEC 62366

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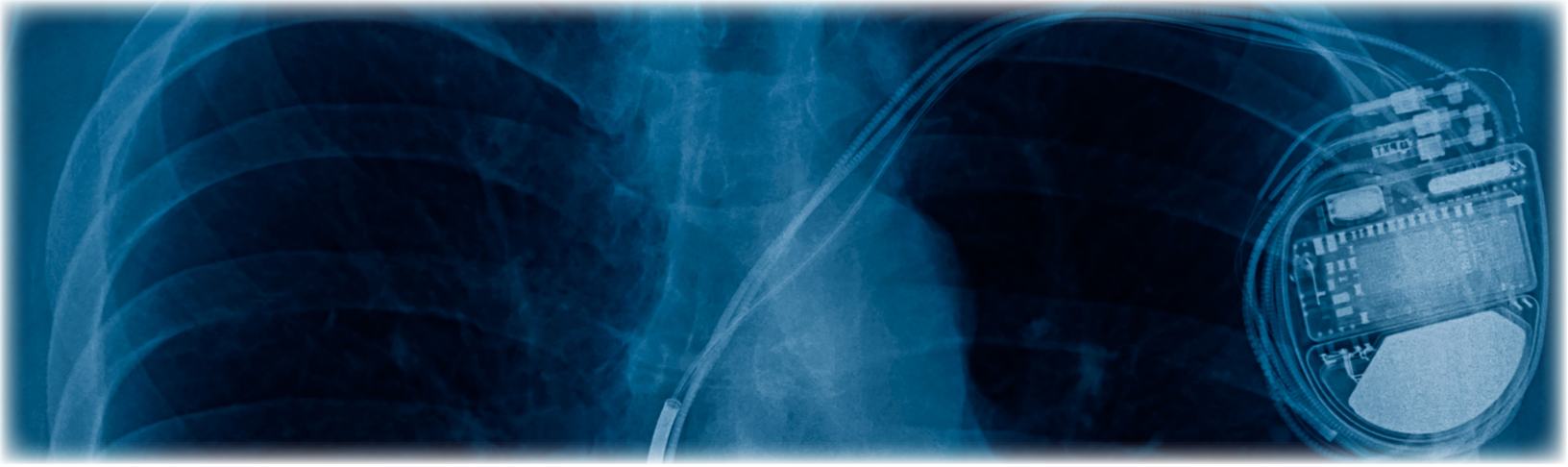
The IEC 62366-1 standard was first published in 2007 and defines the requirements for applying usability engineering to medical devices. The main objective of the standard is to reduce the risks associated with user interaction with the device, ensuring safe and effective use. Usability is particularly important in medical devices, as misuse or user errors can lead to serious incidents or negative outcomes for patients.

In the 2015 version of IEC 62366-1, Annex C was introduced to provide practical guidance and a systematic approach for evaluating existing user interfaces, particularly those that were not developed following formal usability engineering processes. The current and latest version of the standard is the 2015 edition, which redefines and improves many of the usability approaches compared to the initial version.

Annex C was created to address the issue of User Interfaces of Unknown Provenance (UOUP), which are user interfaces with no detailed documentation on their development process or that were not created following modern usability engineering practices. These devices, which are often in use for many years, may pose unknown risks to users and patients.

Annex C allows manufacturers to retrospectively create a usability file, starting with the creation of a Use Specification, using existing documentation, post-market data, complaints, and field reports. The aim is to provide an alternative process that manufacturers can use to identify usability-related risks and propose modifications or improvements to align the devices with modern standards.

In summary, Annex C is a valuable tool for ensuring the safety of legacy user interfaces, enabling manufacturers to adapt existing devices without the need for complete redesigns.



Planning an implantation study to evaluate local tissue effects

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The assessment of local tissue effects after implantation according to ISO 10993-6:2016 is essential to evaluate the interactions of medical devices having direct contact with human tissues during clinical use.

From a regulatory point of view, ISO 10993-6:2016 provides general requirements for evaluating the local tissue effects after implantation of biomaterials intended for use in medical devices mainly in subcutaneous tissue, muscle, bone or brain tissue. This guideline describes biological evaluation in general terms and requires testing strategies that mirror the medical device's intended clinical use without giving detailed test procedures.

The first phase is to define, for a specific medical device, implantation study design recommendations that meet applicable standard requirements (i.e., ISO 10993-1:2018, ISO 10993-6:2016 and ISO 10993-12:2021), along with justifications for the customised test design recommendations to determine the most ethical and cost-effective, but scientifically relevant and regulatory compliant study.

Subsequently, the definition of recommendations for the design of the implantation study prior to the drafting of the study plan and its implementation in animals is of crucial importance. This helps refine testing conditions and save time for further discussions with the testing laboratories in charge of the in vivo testing. In addition, it also facilitates exchanges with competent authorities for in vivo studies, to ensure acceptance of the study design.

Indeed, care should be taken regarding the choice of: animal species selected and number of animals involved, implantation site (tissue), implantation periods (e.g., short-term, long-term), number of samples (i.e., implantation sites) to analyse, sample preparation and evaluation parameters (clinical follow-up, sample collection, microscopic/histological assessment). The choice of control(s) is also crucial. The selection of a relevant predicate (i.e., marketed medical device whose clinical acceptability and biocompatibility characteristics have been established) should be considered (if available). The predicate device is similar to the medical device under evaluation in design, composition and intended clinical use.

Eurofins Medical Device Services can support manufacturers in planning a local tissue effects evaluation, both in terms of study design recommendations and in vivo testing, in accordance with ISO 10993-6:2016.

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