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MEDICAL DEVICE NEWS

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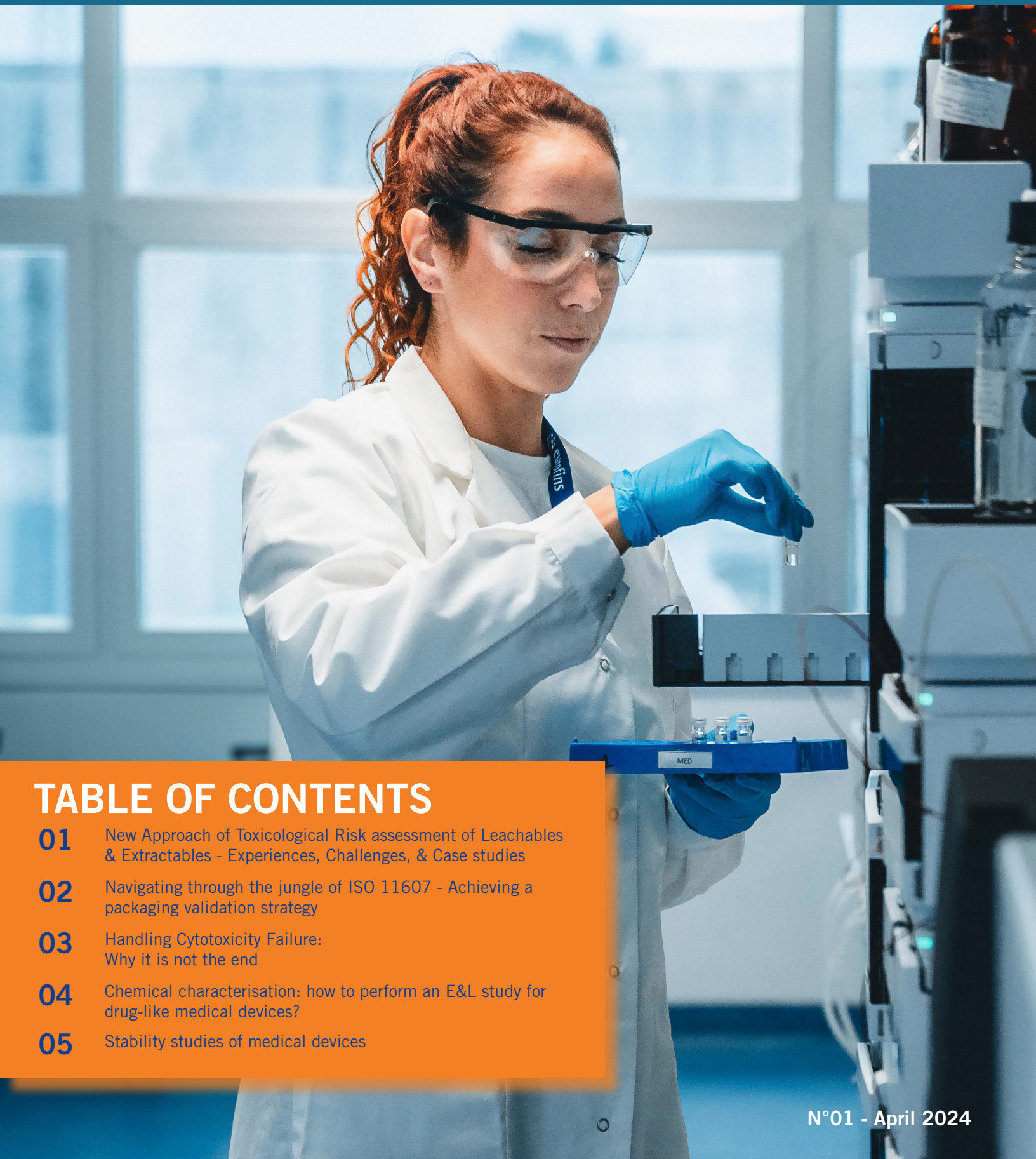

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New Approach of Toxicological Risk assessment of Leachables & Extractables - Experiences, Challenges & Case studies

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As described in ISO 10993-1, the chemical characterisation of medical device constituents is the curial first step in biological safety evaluation. The process of material characterisation should include, as a minimum, an assessment of all constituents of the device, as well as possible residues from the manufacturing process (e.g. processing aids, additives).
A comprehensive chemical characterisation combined with a toxicological assessment might enable the discussion of endpoint covering systemic effects of the biocompatibility assessment.

Toxicological risk assessments (TRA) of medical device constituents must follow ISO 10993-17. The revised ISO guideline 10993-17 was published in late 2023, implementing many changes and new concepts.

According to guidelines, the general process can be divided into two parts: (1) hazard identification by identifying medical device constituents capable of causing harm during the clinical application of the medical device; and (2) estimation of potential risk.
As part of the risk estimation, typically a worst-case estimated exposure dose (EED) for the respective substance under investigation is determined by considering the intended use and clinical scenario of the medical device.

In addition, toxicological thresholds need to be defined to evaluate the constituent-specific tolerable intake (TI). Once the estimated exposure dose and the toxicological threshold have been determined, the margin of safety (MoS) can be calculated in relation to these.
With the help of the MoS, the potential risk of the respective substances within the clinical application of the medical device can be concluded.

In conclusion, a comprehensive chemical characterisation together with a subsequent toxicological risk assessment, excluding the potential risk from leachable and extractable substances within the clinic application of a medical device, can be used for the discussion of certain endpoint tests in the context of the biological safety assessment.
A well-structured and planned chemical characterisation can thereby prevent some of the major problems arising during the toxicological assessment.

Navigating through the jungle of ISO 11607 - Achieving a packaging validation strategy

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Validation of packaging for terminally sterilised medical devices is carried out in accordance with ISO 11607-1 and ISO 11607-2.
The requirements of ISO 11607-1 should already be taken into account during the development phase of such packaging. Important requirements for the packaging material include compatibility with the sterilisation process, biocompatibility, shelf-life studies, and the handling process (aseptically presentation).
In addition to ISO 11607, DIN CEN ISO TS 16775 can be used as a supporting guideline for the validation of sterile barrier systems.

Packaging validation is always machine- and tool-specific. In line with the standard ISO 11607, an IQ (Installation Qualification), OQ (Operational Qualification) and PQ (Performance Qualification) are required for packaging validation as a minimum. The OQ is used to determine the parameter limits and the worst-case cavity. The worst-case seal can also be determined within the OQ. During the PQ, the performance and process capability of the sterile barrier system is verified, by various tests on the nominal parameters.

Tests can include (but are not limited to) seal strength measurement, dye penetration test, visual and manual test, and burst pressure test. The number of samples for the individual tests should be selected and evaluated based on a statistical approach.

In addition to the packaging validation, it's also essential to verify that the sterile barrier system retains its integrity after sterilisation process. Full integrity tests should be carried out for this purpose. Full integrity can be tested by assessing microbiological barrier properties (DIN 58953-6) or conducting a bubble test (ASTM F2096), for example.

Furthermore, a transport simulation should be carried out for the final packaging system, covering the worst-case distribution route and factoring in all necessary climatic conditions. Finally, the safe storage of the packaging system over a specified period of time must be confirmed.

For this purpose, the sterile barrier system should be stored under real-time conditions and then evaluated. To generate initial ageing data, the ageing process of the packaging can be accelerated in accordance with ASTM F1980.

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Handing Cytotoxicity Failure: Why it is no the end

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Cytotoxicity is one of the most common assays performed as a part of medical device biocompatibility assessments. It is described in ISO 10993-5 as one of the "big three" assays used in testing as part of the biological evaluation of a medical device.

There are several methods used to perform this test, the main ones are direct contact and extraction methods. Direct contact involves placing the medical device (or the test item) directly on a cell monolayer, while extraction involves extracting constituents of the device using appropriate extraction media (e.g., a culture medium), time (e.g., 24 or 72 hours) and temperature (e.g., 37°C). Both qualitative and quantitative assessments are performed at the end of the selected contact time. Qualitative evaluation involves a scoring system based on the condition of the cell monolayer. Typically, these are scored from 0 (no cytotoxicity) to 4 (severe), with a cutoff at grade 2. Quantitative assessment objectively quantifies cell viability, with a viability loss over 30% considered cytotoxic. Also in this case, several methods are available with MTT, XTT and NRU being the most common.

A cytotoxic response suggests that a substance released from the test article impacts cultured cells, but it doesn't necessarily mean the device is unsafe for clinical use. Investigating the reasons behind cytotoxicity is crucial and may include examining device materials, manufacturing residues, cleaning processes, or any other aspect which may have altered material chemistry or left residues.

Positive responses in tests require thorough investigation, including checking with the lab, assessing controls, examining sample preparation, and considering the constituents of the device. Chemical characterisation may be necessary to identify leached constituents and assess risks to patients.

Even negative results require scrutiny as changes in device appearance or media observations (cloudiness, particulate, colour change) can require an explanation. Quick chemical tests can help identify issues like the release of particulates or pH shifts.

In conclusion, while cytotoxicity by itself does not necessarily mean a given device will be unsafe, discovery of the root cause of this cytotoxicity is important to either make the case that the device is safe despite this result or if additional changes are indeed needed.

Chemical characterisation: how to perform an E&L study for drug-like medical devices?

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ISO 10993-18 was released in 2020 and specifies how to identify and quantify the constituents of a medical device, allowing the identification of biological hazards and the estimation and control of biological risks from material constituents. When it comes to extraction testing, this standard provides useful guidelines on the solvent, methods and conditions to be used.

A substance-based medical device should approach the chemical characterisation by using the flowchart in ISO 10993-18:2020, starting with information gathering, assessing the exposure to a device constituent and producing data from chemical analyses if needed.
A crucial aspect in determining the need of an additional chemical test is the device risk categorisation. In fact, for higher risk medical devices the amount of chemical data to generate increases.

There are different critical aspects of determining the appropriate strategy for chemical testing of substance-based and drug-like medical devices. Practically speaking, they can be resumed in extraction conditions, solvents selection and compatibility AET (Analytical Evaluation Threshold) calculation, technique standards selection and methods, and in setting appropriate target leachables analyses.

Ensuring the safety of substance-based medical devices relies on selecting the right solvent and extraction conditions. Two kinds of approaches can be applied to this process, each with distinct pros and cons. The composition-centric approach aligns solvent properties like polarity and pH with device constituents, offering direct correlation but potentially facing regulatory resistance due to perceived mildness. Conversely, adhering to ISO 10993-18 introduces stringent conditions in terms of solvents, risking overestimation of extractables.

A third alternative perspective involves a direct leachable approach, mirroring real-world scenarios. However, its universal applicability for initial screenings may be limited only to simple composition due to the compatibility needed between the product and the very sensitive mass detectors adopted for the tests.

Stability studies of medical devices

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Stability studies for medical devices are commonly carried out by manufacturers, although the regulatory and normative framework is not always straightforward.

It is therefore necessary to define the purpose of such a study (shelf-life determination, product quality, supply chain management, etc.) and the type of product concerned (Medical Device, Combined MD or Sterile Barrier System).
A careful review of the applicable regulation (MDR 2017/745, ISO 13485) and standards/guidelines (ASTM F1980, ICH Q1A), which include a risk analysis, should allow a relevant stability study to be designed.

The impact of various environmental conditions (most prominently, temperature and relative humidity) should be assessed, as well as the material characteristics.
The endpoints to be addressed (sterile barrier and micro-organisms impermeability, biocompatibility and toxicology, physical and chemical properties) should be carefully selected, along with the test methods to be validated prior to starting the studies.

Stability studies also allow a better understanding of the degradation mechanisms of the materials and the Sterile Barrier System.

Consequently, it is then possible to collect data before real-time aging results and proceed with any adjustments. It is therefore also important to set different time intervals, especially when trending. After establishing the design of a stability study for a medical device, it is important to monitor the storage conditions and flows related to the study.

These topics should be managed according to the Ishikawa method, which makes it possible to take all aspects into account to carry out the stability study under controlled conditions.

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