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From Guidance to Practice: Translating FDA Draft guidance into Actionable Analytical Strategies Aligned with ISO 10993-18:2020

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Chemical characterisation represents a foundational step in evaluating the biological safety of medical devices.

When existing chemical and toxicological data on raw materials, manufacturing processes—including packaging and sterilisation—are incomplete or unavailable, targeted chemical characterisation studies become essential. These studies are designed to identify extractable and leachable substances and to assess their potential toxicological impact, ensuring compliance with regulatory expectations and safeguarding patient health.

ISO 10993-18:2020 /Amd.1:2022 provides the framework for chemical characterisation within a risk management process. However, it lacks detailed guidance on extraction conditions, procedures, execution of analytical studies, level of identification of compounds and much more.

To address these gaps, the FDA released a Draft guidance in September 2024 titled "Chemical Analysis for Biocompatibility Assessment of Medical Devices." This document offers a more structured and detailed approach to chemical characterisation, particularly regarding extraction protocols and analytical strategies, in support of biocompatibility evaluations.

This white paper outlines the technical steps required to implement the FDA guidance, with a focus on analytical methodologies, data interpretation, and alignment with ISO 10993-18:2020. It also highlights how these requirements have been adopted across the Eurofins Medical Device Services laboratories.

The goal is to provide a clear overview of the most critical elements of the FDA guidance and to demonstrate their practical application in ensuring the safety and compliance of medical devices.

1. Requirement:

More Specific Extraction Conditions

The FDA guidance clearly recommends the use of both polar and non-polar solvents for chemical characterisation of medical devices with limited (≤ 24 h) or prolonged contact (> 24 h up to 30 days). For devices intended for long-term contact (> 30 days), an additional semi-polar solvent is required.

For products with limited or prolonged contact, the guidance advises exaggerated extraction conditions, meaning that both time and temperature should exceed standard parameters to ensure thorough extraction.

In the case of long-term contact devices, exhaustive extraction using Non-Volatile Residue (NVR) analysis is prescribed and may also be applied to prolonged contact devices. NVR-based exhaustiveness defines the number of extraction steps required for the main chemical tests:

- Implants: Minimum of 2 extraction steps, each lasting 72 hours
- All other devices: Minimum of 3 extraction steps, each lasting 24 hours

2. Requirement:

A tabular comparison between the total amount determined by NVR and the total mass from semi-quantification of extractables and leachables by analytical techniques needs to be provided to support the absence of significant loss of extractables during processing and analysis

The total mass from NVR and semi-quantification by analytical techniques are currently reported separately in the study reports of Eurofins Medical Device Services to address this main FDA expectation. However, as there is, to date, no FDA guidance on tabular comparison and how to justify any differences, it has not been implemented yet. This is particularly relevant since these values rarely correspond exactly

3. Requirement:

Triplicate testing is now formally requested for each solvent if not differently justified (even for Exhaustivity determination)

Exhaustivity evaluation thought NVR analysis and the main analytical tests are recommended to be performed in triplicate unless a justification is provided. The extract containing the highest concentration of detected substances is then selected for toxicological evaluation.

Triplicate testing significantly increases the analytical workload, the volume of data generated, and the complexity of toxicological assessment—ultimately leading to higher study costs and duration.

However, triplicate testing may not be necessary when three or more devices are pooled for the extraction study. In such cases, a single extract per solvent is typically sufficient for both Exhaustivity assessment analysis and chemical testing.

The Eurofins Medical Device Services laboratories offers single and triplicate testing and upfront discussion about necessity of triplicate testing and/or options to reduce sample numbers in case of very expensive products.

4. Requirement:

Pooling of extracts (iterations) previously not recommended by the FDA is now accepted

It is not possible to predict the number of NVR cycles required to achieve exhaustiveness, nor the extraction volume needed for AET calculation. Additionally, this approach is only possible when the theoretical AET is sufficiently high. Therefore, our standard practice is to perform analyses at each time point rather than using a pooling strategy, which can significantly impact final costs.

Moreover, recent feedback from the FDA indicates that while pooling is technically acceptable, it is not a preferred approach. However, on client request, pooling the extracts can be evaluated (in relationship to AET value).

5. Requirement:

Swelling of test articles as sign for solvent incompatibility or is swelling acceptable?

Previously, visible degradation of test samples during extraction — such as swelling, turbidity, or particulate formation — was considered as indication of incompatibility between the test article and the solvent. However, the FDA now distinguishes between “destructive” and “acceptable” swelling, stating: “Some swelling of test articles is expected and is acceptable if the test article remains intact.”

Eurofins Medical Device Services laboratories conduct solvent compatibility pretests to assess potential interactions. Study reports include pictures of both the test samples and extracts, along with a description of observed degradation parameters.

6. Requirement:

Neat extraction solvents, alcohol as semi-polar solvent, to be preferred to alcohol-water mixtures

The FDA prefers the use of pure solvents for chemical extraction. In cases of solvent incompatibility, two alternative solvents of the same polarity must be tested to ensure adequate extraction.

Eurofins Medical Device Services laboratories have validated numerous solvents of different polarities to be prepared for solvent incompatibilities.

For semi-polar solvents, our laboratories typically use neat solvents such as isopropanol, ethanol, or acetonitrile. However, if none of these pure solvents are compatible with the test article, it becomes necessary to switch to alcohol/water mixtures as an alternative.

7. Requirement:

Extraction with water for elemental analysis, acidic conditions may be used to maximise analyte release

For ICP-MS analysis the standard approach is to use water for ICP-MS. The samples are acidified before the test (prior to injection).

8. Requirement:

Extractions above clinical use temperature: Justification needed in case of visible changes (thermal damage and/or solvent incompatibility) to lower temperature

Temperature and duration shall be exaggerated compared to clinical conditions. If elevated temperatures cause thermal damage or solvent incompatibility with three solvents from the same polarity, the extraction temperature may be reduced, but not less than in the clinical application. Test materials can be extracted at two different temperatures using different solvents. Pretest results indicating solvent incompatibility are referenced in the analytical testing study plan for justification.

9. Requirement:

Sensitivity of the analysis methods (e.g. limit of detection (LOD), and limit of quantification (LOQ)) should be established, LOQ for each reference standard should be lower than the reporting threshold (e.g. AET)

Calculating the Analytical Evaluation Threshold (AET) is essential, as all substances detected above this threshold are subjected to toxicological risk assessment. The AET determination is described in detail in the study plan, including an explicit statement on whether the AET is equal to or above the limit of quantification (LOQ). If the AET falls below the LOQ, adjustments such as extract concentration or changes in extraction volume may be applied. When such adaptations are not feasible, a full justification — such as using the limit of detection (LOD) as the reporting limit — is provided in the study plan by Eurofins Medical Device Services laboratories.

10. Requirement:

Requirement: Include parameter D to account for extract processing in the equation to calculate AET

The parameter D is the dilution or concentration factor (i.e., D = Vfinal/Vinitial). If the extract is diluted, D > 1. If the extract is concentrated, D < 1. If the extract is not processed, D = 1 and inclusion of the parameter D is optional for AET calculations. Thus, dilution of an extract results in a lower AET value and concentration of an extract results in a higher AET value in comparison to an unprocessed (D = 1) extract.

Concentration of the extract has been validated by Eurofins Medical Device Services laboratories to prove that no compounds are lost e.g. by evaporation.

11. Requirement:

All extract processing needs to be qualified with a dedicated spike and recovery verification study, recoveries should be between 80-120%

The recovery verification studies have been performed for a list of references/surrogates. A comprehensive set of solvents are available and concentration has been validated. New internal standards will be introduced to “adjust” the concentration obtained.

12. Requirement:

Identification of extractables should be confident or confirmed to be adequately used for TRA, unknowns or Tentative identification should be justified with a specific list of elements provided in the guideline

As there is a broad variety of determining the levels of identification between laboratories, the FDA guideline suggests a differentiation of confirmed, confident, tentative and unknown compounds which is a major step towards standardisation for toxicological risk assessment. Nevertheless, tentative identification and unknowns will still occur, though Eurofins Medical Device Services laboratories have an already extensive database for identification of substances. Toxicological approaches considering already available information about the medical device, composition, manufacturing process etc. are used to estimate the risk for the patient or suggest further procedure to mitigate the risk. In terms of analytical examination of tentative and unknown substances there will be further discussion and development on how to improve and deal with these compounds in future.

The Draft FDA Guidance “Chemical Analysis for Biocompatibility Assessment of Medical Devices” provides comprehensive direction on extraction procedures, analytical testing, and result interpretation.

By offering detailed methodologies, it supports greater consistency and standardisation across laboratories. However, as this guidance remains in draft form, it continues to receive substantial feedback from stakeholders. Revisions and further developments are anticipated, reflecting the evolving landscape of regulatory expectations and scientific advancements.