SPOTLIGHT feature

Clinical, Medical & Diagnostic Products

Navigating the Complexities of E&L Analysis in Medical Devices

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The growing complexity and diversity of medical devices have increased the demand for advanced and specialised testing to ensure the safety of medical devices. Chemical characterisation of product materials (polymers, metals, ceramics) and extractables and leachables (E&Ls) is crucial in assessing the potential impact of the medical device's biocompatibility and the associated toxicological risk.

Medical devices should not release chemicals that can accumulate or leach into the human body in amounts significant enough to pose a risk of toxicity or impact its stability and effectiveness. Throughout the lifecycle of a medical device, from manufacturing to storage, there can be intentional or unintentional addition of compounds. E&L analysis is performed on all medical devices from simple tongue depressors to more advanced pacemakers to identify potentially toxic chemical compounds present in the device. Given the diverse chemical structures and additives that can leach out of manufacturing or packaging components, it is increasingly challenging to identify and precisely quantify E&Ls accurately.

Challenges of E&L Analysis

Accurate identification of E&L compounds is essential to ensure the safety of medical devices. However, there are many challenges to understanding E&L information.

Processing and Data Management

Different solvent and extraction conditions must be used for each sample, and it can take a long time to process, analyse, and report these studies. This also generates a significant amount of data which must be appropriately managed and stored.

Detection and Identification

The complexity of materials used makes identification challenging, as E&Ls are often unfamiliar compounds lacking available reference standards. Detection can be masked due to extremely low concentrations of leachables, or secondary degradants can form over time making identification difficult. It is important to determine correct dose-based thresholds, this usually requires toxicologist input.

Ambiguity in Guidelines

While there are existing guidelines for E&L analysis, they can be ambiguous - leaving scientists uncertain about whether they have fulfilled all the necessary regulatory requirements. Scientists do the most they can, in the allocated time, but are often left feeling that it's not enough for regulatory approval.

Regulatory and Advisory Guidelines

In recent years, regulatory and advisory bodies have significantly increased their attention to the characterisation of chemicals and their focus on quality control. While there is some ambiguity, there are consistent guidelines for all medical devices. The ISO10993-18:2020 guidelines are a set of standards that guide the process of characterisation for medical devices. These guidelines cover the identification of the materials of construction, clarify extraction procedures and analytical techniques to be used in E&L testing, and have an annex dedicated to the analytical evaluation threshold (AET). The AET is calculated based on the dosage and the route of administration. Chemical species detected at or above this threshold need to be identified, quantified, and reported for possible toxicological assessment. Setting and meeting the AET is an important part of the regulatory submission process.

Analysis of E&Ls

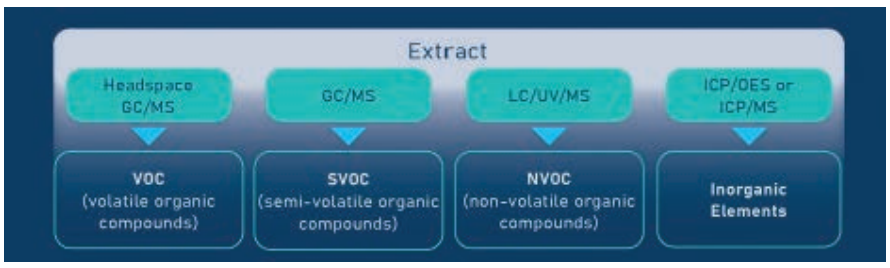
The presence of E&Ls in medical devices after the manufacturing, packaging, or storage process is unavoidable. E&L analysis is crucial for evaluating the potential toxicological risks these E&Ls may pose to human health. E&L studies require careful design and must consider factors such as the device's classification, intended use, and duration of contact. The setup of a chemical characterisation study can be summarised in three steps - extraction, detection, and identification and quantification.

Extraction

Compound discovery and identification are performed to extract the largest amount of extractable for identification. The type of extraction (exaggerated, exhaustive, or simulated use) and the conditions (extraction solvent, temperature, and time) selected depend on the type of medical device to be tested.

Detection

There are different techniques to use for the chemical characterisation of E&Ls. To choose the correct technique for analysis, it must be clear which compounds will be analysed. Compounds that can potentially be harmful and the tests required for analysis are shown.



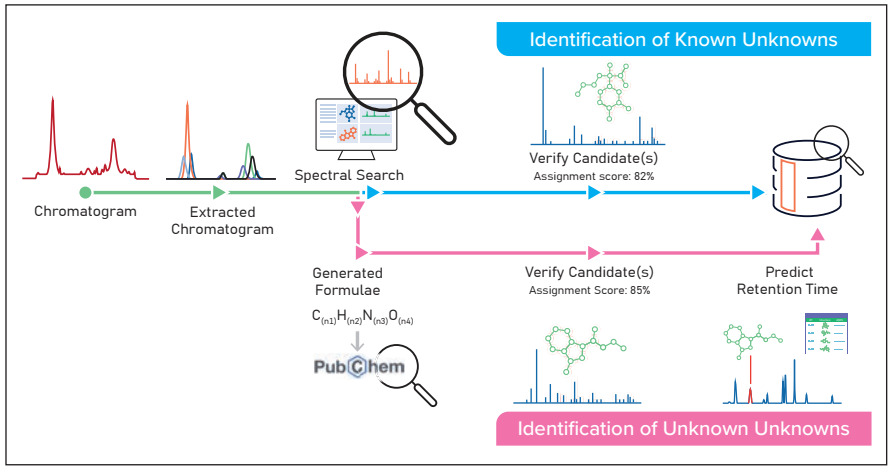
It is also important to consider how the analytical technique will be applied and decide whether to take a screening approach (screen for every potential compound present in the extract) or a targeted approach (detect what is known with a low limit of quantification (LOQ) and high accuracy). To ensure all compound classes and ionisable species are covered, it may be necessary to use multiple analytical techniques (including high-sensitivity instruments).

Identification and Quantitation

Targeting methods and real-use conditions indicate true concentration exposure, allowing toxicological assessment on realistic values—testing the actual impact and the products. Compounds detected at or above their toxicological thresholds are targeted for identification and quantification.

Identifying every analyte is not always possible, and consideration must be given to unknown compounds. These unknown compounds have the potential to impact the safety of the medical device. Furthermore, it is not possible to confirm every single identification with authentic reference sources. To sufficiently identify and report E&Ls, it is necessary to establish and utilise levels of confidence.

Software programs like ACD/Labs' MS Structure ID Suite analyse and process xC/UV/MS data and store the knowledge in searchable databases. MS Structure ID Suite uses analytical chemistry to identify and quantify E&Ls - enabling confident identification of ions present in the spectra, assisting with fragment assignment, and quantifying these analytes.



Accelerate E&L Component Characterisation

MS Structure ID Suite software helps accelerate component identification for both LC/MS and GC/MS data. The various tools in the software help elucidate each component structure efficiently and confidently. For known E&Ls, the semi- or fully automated workflow isolates compounds and searches databases to identify and list all possible candidate structures, conducting spectral comparison via mirrored plots (mass difference) and determining a hit quality index. Automated assignment then further verifies top structure candidates by determining an assignment score and showing structural fragments and a match factor for experimental spectra.

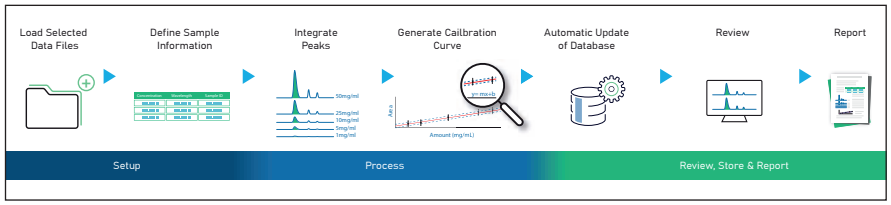
For true unknowns, you can use the Molecular Formulae Generator to propose potential molecular formulae and then search for a target component's accurate parent mass and predicted molecular formula to generate a ranked structure hit list. Predicted fragments are then matched to experimental spectra with automation and an additional check can be performed to predict retention time based on structural similarity to known components.

The chemical characterisation workflow consolidates analytical and metadata in a centralised database for easy access to information necessary for regulatory documentation and to comply with regulatory requirements, including ISO10993:18 (2020), 21 CFR Part 11 (i.e., traceability, audit trail, etc.).

Accurate Quantitation of E&Ls in Compliance with Regulatory Guidelines

Traditionally single-point calibration has been used with a single reference standard (also referred to as estimated quantitative analysis). In ISO10993-18:2020, an updated definition of semi-quantitative analysis has been added where the quantitation is based on the relative responses of the analyte and the surrogate reference standard, and it is now common practice for regulators to expect multiple concentration levels of standards.

After identifying E&Ls at or above the AET, accurate quantitation is essential. MS Structure ID Suite offers a comprehensive LC/MS and GC/MS quantitation workflow. All xC/UV/MS data can be processed and quantitated efficiently and accurately in a single interface - minimising transcription errors and ensuring consistency and standardisation in quantitative analysis. Using the workflow, unknowns are quantitated against the set of standards - peaks are identified, and peak detection and integration parameters are applied to generate a calibration curve.



Accelerating E&L Studies with Effective Knowledge Management

Managing large volumes of data is very difficult without a well-organised system in place. Database curation allows users to find the right data at the right time—helping to ensure data is accurate, high quality, relevant, and easily accessible.

Errors in the identification of E&Ls can result in flawed safety and biocompatibility assessments. Accurate identification of E&Ls is made challenging by the lack of availability of authentic reference standards. To overcome this challenge, it is essential to create comprehensive proprietary databases. Having a comprehensive repository with the highest possible number of verified identifications enables quick and confident identification of both known and unknown E&Ls. Database curation minimises the duplication of work, saves time, and resources, and protects valuable data assets.

The presence of E&Ls is inevitable, emphasising the importance of assessing potential toxicological risks. E&L studies aim to test both extractables (the possible impact and materials of medical devices) and leachables (the actual impact and the products) to ensure the safety of the device. The accurate identification and quantification of E&Ls is challenging and there are many uncertainties in E&L analysis regarding the application of reference standards, reliability in identification, and correct selection of dose-based thresholds. Some of this can be mitigated with the use of software solutions, like MS Structure ID Suite, which can help to ensure the precise identity and quantity of E&Ls found in all classes of medical devices - helping to safeguard patients.

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