Into the Unknown: The Analysis of E&Ls in Medical Devices

As the complexity and variety of medical devices have increased, so has the demand for advanced and specialized testing to safeguard patients. Many factors make extractables and leachables (E&Ls) analysis challenging.

Software solutions, like MS Structure ID Suite, can help to determine the precise identity and concentration of E&Ls found in all classes of medical devices—ensuring that analytical knowledge is retained and can be leveraged in the future.

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Challenges of E&L Analysis

Ensuring the precise identification of E&L compounds is crucial to ensure the safety of medical devices. However, there are many challenges involved in understanding E&L information.

Processing Time
It can take a long time to process, analyze, and report studies—especially as replicates must be analyzed in different solvents and extraction conditions

Complexity of Materials
Increasing complexity in the types of materials used means that E&Ls are often unknown compounds without available reference standards

Data Management
A significant amount of data is generated which needs to be appropriately managed and stored

Hampered Detection
Leachables migrating into drug formulations over time form secondary degradants or leachables are masked due to extremely low concentrations

Correct Thresholds
Toxicologists need to be involved in determining the Analytical Evaluation Threshold (AET)

Analysis of E&Ls

The infiltration of harmful chemicals into the medical device during the manufacturing, packaging, or storage process is inevitable. E&L analysis aims to identify and assess whether these chemicals pose any toxicological risks. Toxicology focuses on identifying the baseline concentration threshold (AET) at which chemicals should be identified and reported.

E&L studies require careful design and depend on the *class* of device, *use* of the device, and *contact time*. The correct technique for analysis must be selected and multiple analytical techniques may be required to cover all compound classes. The analysis of E&Ls is a two-step process:

1. Extractables—Compound discovery and identification by extraction (exaggerated, exhaustive, or simulated use conditions) to extract the largest amount of extractable for identification. This tests the possible impact and the materials.

2. Leachables—Quantitation of concerning compounds in the drug itself, targeting compounds detected at or above their toxicological thresholds. Targeting methods and real-use conditions indicate true concentration exposure, allowing toxicological assessment on realistic values. This tests the actual impact and the products.

Chemical Characterization

Chemical characterization of product materials (polymers, metals, ceramics) and E&Ls is crucial in assessing the potential impact of the medical device's biocompatibility and the associated toxicological risk.

Supports biocompatibility testing

Reduces time and cost

Reduces animal testing

Given the complexity and diversity of medical device E&Ls, 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 utilize levels of confidence. The USP 1663 recognizes three identification categories: tentative, confident, and confirmed.

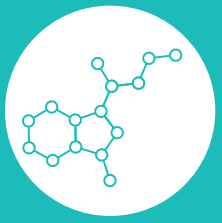
Software programs like ACD/Labs' MS Structure ID Suite use analytical chemistry to *identify* and *quantitate* compounds in or on medical devices—enabling confident identification of ions present in the spectra, assisting with fragment assignment, and quantifying these analytes.

Accelerate Chemical Characterization with Software

Various tools in MS Structure ID Suite software help accelerate component identification for both LC/MS and GC/MS data.

Quickly search a wide range of potential structures

Curate a reasonable and relevant list of structure candidates

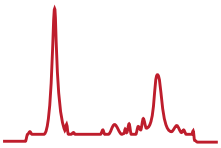


Identify the most likely structure

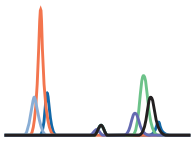
Elucidate each component structure efficiently and confidently with a workflow that:

- Can be semi or fully-automated for improved efficiency
- Complies with regulatory requirements, including ISO10993-18[1], 21 CFR Part 11[2] (i.e., traceability, audit trail, etc.)
- Allows easy access to information necessary for regulatory documentation
- Consolidates analytical and metadata in a carefully curated centralized database

Workflow for Identifying Known E&Ls

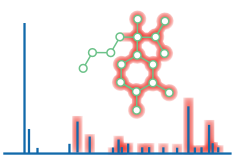


Chromatogram



Extracted Chromatogram

Spectral Search



Verify Candidate(s)

Assignment score: 82%

MS Structure ID Suite software is vendor-neutral and multi-techique and used to import all xC/MS data. The various tools within the software assist with spectral interpretation and fragment assignment—instilling confidence in the assignment.

The Intelligent Component Recognition (IXCR) tool is an automated workflow to isolate components and search databases (Wiley, NIST, and user-created MS databases) to identify and list possible candidate structures. It is used to:

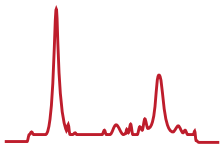
- Conduct spectral comparisons via mirrored plots (mass difference)
- Determine a hit quality index (HQI%)

Depending on the HQI%, if further verification of known compounds is required, the AutoAssignment tool is used to interrogate LC/MS^n data and top structure candidates to:

- Determine an assignment score
- Show structural fragments and match factor for experimental spectra

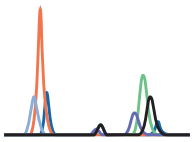
Workflow for Identifying Unknown E&Ls

Following IXCR screening, for cases of true unknown components, the workflow consists of:



Chromatogram

Propose potential molecular formulae and display expected isotopic abundance using the Molecular Formula Generator tool.

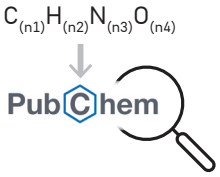


Extracted Chromatogram

Search for a target component's accurate parent mass and predicted molecular formula to generate a ranked structure hit list.

Spectral Search

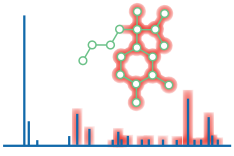
Use the AutoAssignment tool to match predicted fragments to experimental spectra—using the assignment score to help determine the best structural matches.



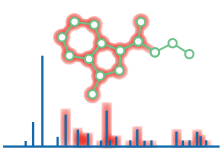
Generated Formulae

Perform an additional check with the ChromGenius tool to predict retention time based on structural similarity to known molecules.

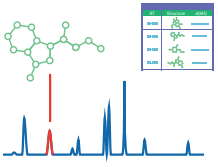
Curation of a Centralized Database: Once an accurate structure verification is achieved, the associated analytical and metadata are stored in a centralized database. Scientists have access to live, curated data from any remote location, allowing cross-functional teams to work and make decisions more efficiently.



Verify Candidate(s)
Assignment score: 82%



Verify Candidate(s)
Assignment Score: 85%



Predict Retention Time

The Importance of Database Curation

Carefully curated databases allow the *right data* to be found at the *right time*—ensuring that data is:

- High-quality
- Relevant
- Accessible
- Secure

The lack of availability of authentic reference standards creates challenges in the chemical characterization of E&Ls. This can result in erroneous identification leading to compromised safety and biocompatibility assessments and disapproval of regulatory submissions. These issues can be prevented by creating comprehensive proprietary databases of E&L compounds with the highest possible number of verified identifications.

Using MS Structure ID Suite, disparate data can be united making it easily accessible and usable. The creation of a comprehensive repository enables quick and confident identification of E&Ls, saves resources, and minimizes the duplication of work.

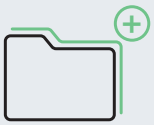
Quantitation of E&Ls

E&L impurities in medical devices can pose potential safety risks based on toxicity and concentration levels. After identifying E&Ls at or above the AET, accurate quantitation is essential to determine the concentration for safety assessments.

MS Structure ID Suite offers a comprehensive LC/MS and GC/MS quantitation workflow for medical device E&L testing. All xC/UV/MS data can be processed and quantitated efficiently and accurately in a single interface, ensuring:

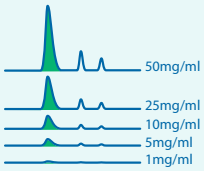
- Connectivity between data and numerical results
- Consistency and standardization in quantitative analysis
- Minimal risk of transcription errors as the workflow is completed within a single software

Quantitation Workflow

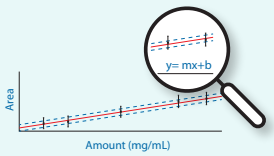


Load Selected Data Files

Define Sample nformation



Integrate Peaks



Generate Cailbration Curve

Automatic Update of Database

Review

Report

SET UP: Define sample information including *sample type* (i.e., standard, unknown), *type of trace* (i.e., XIC, flat chromatogram, DAD), and the *compound(s)* for quantitation.

PROCESS: Quantitate unknowns against the set of standards to determine the amount of analyte present.

- Identify peaks for quantitation
- Apply peak detection/integration parameters and generate a calibration curve with a regression line, standard deviation, and r^2
- Use the analysis of residuals to determine the suitability and validity of the statistical regression model

REVIEW, STORE & REPORT: The full set of data (raw and processed) is automatically saved to a database.

- View and modify results and track changes made in the processing interface for data integrity purposes
- Store and visualize data
- Create and share reports

Meet the Scientist

Cindy Roberson
Principal Chemist
Medtronic

In 2017, the Medtronic team had an unexpected opportunity to rethink the hardware and software used for their E&L studies. They were faced with a pressing need to change their analytical data acquisition and processing software. ACD/Labs' MS Structure ID Suite was selected as it met all their requirements, with further scope to grow to meet their evolving needs.

Cindy explains the several requirements that Medtronic was looking for in their new software:

- It was crucial that they operate in accordance with ISO10993-18 and with 21 CFR Part 11 (including traceability, audit trail, versioning, electronic signatures, etc.).
- Be able to curate several libraries/databases with confidence in the identification of known and unknown components.
- Be vendor-neutral and instrument-agnostic. With a variety of instruments across their labs, this was necessary for flexibility in instrument selection both now and in the future.

Confident Identification of Known & Unknown Components

In accordance with ISO10993-18, Medtronic conducts E&L studies to create a profile for every medical device they supply. The team analyzes samples using various techniques (i.e., LC/MS, GC/MS) to elucidate and quantify each component's structure. They use MS Structure ID Suite for their characterization workflow to accurately assign structures for known and unknown E&L components.

Curating Relevant Spectral Data Libraries

The team is responsible for curating spectral databases for LC/MS data from reference standards and materials. Careful consideration is given to the data saved in the libraries and as much data and metadata as possible is included. The archived analytical data is traceable and complies with 21 CFR Part 11 data integrity rules, and information necessary for regulatory documentation can be easily accessed and reported.

> "We chose ACD/Labs' enterprise software because it enables us to create a curated spectral library. It has significantly improved our efficiency and confidence in structure identifications and reduced the possibility of false structure characterization.[3] – Cindy Roberson"

By selecting the right software for their requirements, the team at Medtronic has experienced greater efficiency and confidence in their structure verification. They have maximized the software's use and incorporated it into their future growth.

Regulatory and Advisory

In recent years, regulatory and advisory bodies have significantly increased their attention to the characterization of chemicals and their focus on quality control.

BioPhorum

ELSIE Extractables and Leachables Safety Information Exchange

BPSA

Guidelines of particular interest:

ISO10993-18:2020[1]

A set of standards that guides the process of characterization for medical devices, including:

- Identification of the materials of construction
- Characterization of the chemical constituents, extraction procedures & analytical techniques used
- Reporting information about chemical constituents to support the evaluation of potential patient risk

US Pharmacopeia (USP)

Chapters that provide E&L guidance for medical devices include:

- 1663[4]—Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- 1664[5]—Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

Other Resources

Watch

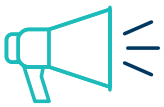
Presentation: A Chemical Characterization Workflow to Improve Confidence in Identification of Unknowns

In this presentation, Medtronic analysts discuss LC/MS-based compound characterization of extractables and leachables supported by effective data management.

Read

Blog: How AstraZeneca is Managing Their Extractables and Leachables Data

Read the interview with Stephen Warren, Associate Director in Inhalation Product Development at AstraZeneca. Stephen delves into how AstraZeneca is getting control of extractables and leachables data.



Read

Press Release: ELSIE Consortium and ACD/Labs Announce Partnership to Develop Safety & Materials Database for E&L Research

ACD/Labs combine their expertise in chemical information management with the knowledge and expertise of ELSIE consortium members to create a searchable knowledge repository of pre-competitive data.

Software solutions can help to ensure confident identification and accurate quantitation of all classes of E&Ls found in medical devices. Contact us to find out further details about how MS Structure ID Suite can support E&L analysis.

Contact Us

References

1. ISO10993-18. (2020). Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process
2. FDA. (2003). 21 CFR Part 11., Electronic Records; Electronic Signatures—Scope and Application
3. Roberson, C. Buchman, J. (2022). A Chemical Characterization Workflow to Improve Confidence in Identification of Unknowns. Watch the webinar
4. US Pharmacopeia (USP). (2015). <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
5. US Pharmacopeia (USP). (2015). <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems