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CASE STUDY 000503

How SGS cut their extractables and leachables workflow time in half using high-resolution analytical methods

The SGS Health Science Fairfield, New Jersey laboratory, a top-tier extractables and leachables (E&L) testing facility, underwent a sequential technology upgrade to implement high-resolution methods that would expand its technical capabilities. The result:

- Higher-quality outputs as unknown analytes are confidently and accurately identified
- A site-wide boost in productivity, with workflow times cut in half
- Additional revenue potential as projects are completed faster

Introduction

With decades of experience in pharmaceutical outsourcing, SGS is a world-leading inspection, verification, testing and certification company with sites spread across the globe. Of the many services offered, the company is an authority in extractables and leachables (E&L) testing.

One of the global centers for E&L testing is the SGS Health Science site in Fairfield, New Jersey, USA. This high-throughput facility runs more than 100 projects annually, with 20-30 projects underway at any given time. The analytical services offered cater to the E&L testing needs of diverse industries, including pharmaceutical, medical device and biotech.

To examine and identify all possible impurities and toxins across different types of matrices, the team at SGS Health Science employs various analytical methods to perform a range of tests.

- **Non-volatile impurity testing:** Liquid chromatography coupled with mass spectrometry (LC-MS) or tandem mass spectrometry (LC-MS/MS)
- **Volatile and semi-volatile impurity testing:** Gas chromatography coupled with mass spectrometry (GC-MS)
- **Elemental impurity testing:** Inductively coupled plasma spectroscopy (ICP) and ICP-MS

As a high-functioning contract research organization (CRO), a prerequisite for the SGS Health Science facility is to confidently profile unknown analytes or accurately match known analytes to an existing library. This makes it necessary to use sensitive and high-resolution methods, and regularly improve workflows as technologies advance.

In recent times, the SGS Health Science facility sought to upgrade its analytical instruments to boost operational efficiency and meet the increasing demand for E&L testing, all while complying with stringent regulatory requirements.

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"In a typical E&L testing program, we first perform extraction on the material and then test for the full spectrum of volatile organic compounds, semi-volatile and non-volatile compounds, and also perform a thorough elemental impurity profile," says Dr. Dujuan Lu, Manager/Global Leader, Extractable and Leachable (E&L) Testing at SGS Health Science. "Every sample we process goes through headspace GC, direct injection GC, LC and ICP analysis along with MS, to avoid missing anything."

— Dr Lu

Why E&L testing requires comprehensive, reliable and sensitive methods

The importance of E&L testing

E&L testing detects potential toxins that may release from pharmaceutical drug products or medical devices that make them unsafe for patient use. Chemicals can leach out from the drug packaging material, the medical device material or can enter through external production processes.

Detecting extractables and leachables is an integral step in analytical testing, as a drug product or device should ideally not release any toxic material that can pose safety risks to patients upon consumption or use. Equally, the leached compounds should not interact with the active pharmaceutical ingredient (API) and, in turn, influence the drug's stability or efficacy.

In addition to detecting traces of these chemical species, the composition of the substance also needs to be identified. Once the analyte is quantified, a toxicological assessment is performed to evaluate the risk of patient exposure. The in-depth analytical process for E&L testing, therefore, requires reliable and sensitive methods.

Full-profile testing is required

Regulatory agencies require full profiling of all E&Ls on every drug product and medical device. This means CROs need to have comprehensive technical capabilities that span the breadth of testing to capture a wide range of analytes, as well as the depth to accurately quantify each impurity. Moreover, sample preparation protocols need to be optimized for a variety of complex matrices.

Regulations are ever evolving

"In the past decade, regulatory authorities have focused more on E&L testing, making it a mandatory step," adds Dr. Lu. As newer impurities get reported, regulations will continue to impose stricter mandates. As such, testing centers need to be equipped with instrumentation that can keep up with evolving regulations and reliably meet the required standards of testing.

Identifying unknowns with confidence: instrumentation upgrade at SGS Health Science Fairfield Laboratory

Unknown identification

One of the big analytical challenges with E&L testing is identifying the chemical species when background details are not known. In these instances, every compound above the safety threshold needs to be identified and quantified. Currently, there are no commercially available compound libraries for LC-MS methods, making it challenging to confidently identify an analyte and perform a safety assessment. For GC-MS, although there are compound libraries available, they often aren't comprehensive. "Even if the unknown compound gets a 90% match based on its mass spectrum, it doesn't guarantee its accurate identification," explains Dr. Lu.

A 'tentative unknown' result can often prompt toxicologists to assume high toxicity levels as a safety measure against potential adverse effects. "Within the same class of compounds, there can be different toxicity levels. In these instances, the concentration of the analyte can make a big difference," says Dr. Lu. "When tentative information or broad chemical classes are used to make safety assessments, it can yield the wrong pathological conclusion, and directly impact the drug or device application status."

To address this challenge and further enhance the capabilities on-site, the SGS team upgraded their workflows to include high-resolution MS instruments that made it possible to accurately identify unknown analytes.

“It’s important for us to stay on top of this changing regulatory landscape and promptly implement any necessary modifications to our protocols,” says Dr. Lu.

Additionally, in a facility that serves a variety of industries, rather than having to process each sample matrix for specific end-point analyses, employing high-resolution mass spectrometry would enable the technical staff to adopt a non-selective, unbiased approach to both sample preparation and analyte detection.

Instruments installed

Over the last few years, the SGS Health Science Fairfield site has implemented technology upgrades to tackle unknown identification in E&L testing as well as improve its overall technical capabilities. To enable full profile E&L testing, both LC and GC systems were replaced with more advanced instruments.

- **LC-MS upgrade:** This involved installing the Thermo Scientific™ Q Exactive™ Plus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer
- **GC-MS/MS upgrade:** This involved installing the Thermo Scientific™ Q Exactive™ GC Orbitrap™ GC-MS/MS system

For both implementations, instruments onboarded into the SGS Health Science E&L facility needed to meet the following performance criteria:

- **High resolution** to detect unknown analytes in the absence of compound libraries
- **High sensitivity** to quantify traces of impurities at sub-ppb levels
- **High robustness** to handle fast-paced, high-throughput workflows in a busy CRO
- **Good manufacturing practice (GMP) compliant** to meet the regulatory standards and uphold data integrity across the facility

Benefits of high-resolution E&L testing

The high selectivity and better resolving powers offered by HRAM MS yielded additional information on the chemical species detected in every sample. As such, it was possible to obtain the accurate mass of the ion fragment and identify the compound. This resulted in **higher quality output** for the site, overall.

The technical team experienced **greater confidence** with E&L testing as the chemical composition of the analyte became available and, in turn, made for more informed safety assessments. When necessary, a tandem MS (i.e., MS^2 analysis on a subset of fragments) could be readily performed to further break down the compound cluster and acquire structural information. Moreover, the high resolving power of the systems significantly removed isobaric interferences, thereby, making it easier to analyze samples in complex matrices.

With **a higher sensitivity** of measurement, the upgraded instruments can now achieve ppb or sub-ppb levels of detection, where previous methods only went down to ppm levels. This is made possible using the

Benefits of implementing high-resolution systems for E&L testing

Workflow times reduced by half

Faster project turnarounds

Higher revenue-generating potential

Competitive advantage over other E&L testing centers

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full- and all-ion fragmentation (AIF) scan modes during LC-MS analyses, and electron ionization (EI) or chemical ionization (CI) scan modes during GC-MS runs. As a result, low abundance compounds can be identified with more certainty. In fact, the LC-MS systems offer an intrascan dynamic range of more than four orders of magnitude, allowing the detection of trace-level and high-abundance compounds in the same scan.

The site also experienced a boost in productivity. In the updated LC-MS workflow, a single sequence covers both positive and negative polarity modes, i.e., instead of running them one after the other, they now run in parallel. **This reduced the workflow time by half.** The rapid polarity switching also enabled all sample data to be captured during a single run, thereby, making retrospective data analysis possible without having to re-run samples.

In addition to being able to identify unknown analytes with ease, using the Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) software on both the LC-MS and GC-MS systems made it easier to implement workflows, troubleshoot protocols and process data. **Projects are now completed at a faster rate, making room for additional projects,** and in turn, generating more revenue for the business.

In summary, the technology upgrade has allowed the SGS Health Science laboratory to provide reliable, rapid and in-depth results to its customers by identifying and quantifying unknown toxins at sub-ppb levels. This has helped the company gain competitive advantage and remain at the top of its industry.

Close collaboration with the Thermo Fisher team for continued success

A dedicated application scientist helped the SGS team set up the equipment and optimize the site's protocols with minimal downtime. Ensuring an active CRO doesn't experience severe interruptions during an instrument upgrade is one of the many factors carefully considered during the installation process.

"As we weren't familiar with the equipment, it was very helpful having a local application scientist train us on it. One of our main goals was to have a fully functioning high-resolution system that offers good sensitivity. With these instruments now installed and in active use, we already consider this collaboration a success," says Dr. Lu.

By choosing to upgrade its analytical technologies and continually improve its processes, the SGS Health Science Fairfield facility has succeeded in accelerating its operational efficiency and revenue. More notably, it is able to perform every E&L test with heightened confidence and continues to serve its clients with unrivaled excellence.

Find out more at
www.thermofisher.com/powerofpartnership

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