A New Era of E&L Analysis

Extractables and leachables testing is essential for small molecule and biopharmaceutical products alike, but it can be challenging, especially for companies with less experience. Are you making the most of technological advances that can make analysis easier – and your drugs safer?

Kyle D'Silva

Andrew Feilden

Most professionals in the pharma industry will have at least a working understanding of extractables and leachables (E&L) – but fewer are so confident on the regulatory requirements with regards to analysis. In simple terms, E&L testing focuses on identifying chemical species that can enter drugs from manufacturing components, packaging and drug delivery systems – but the reality is more complex, particularly when it comes to identifying exactly what limits of detection must be met and what data needs to be provided.

According to Andrew Feilden (Chemistry Operations Director at Smithers Rapra, a consultancy agency focused on rubber and plastics) at its heart, E&L testing is about making products safer. "Some people understand the topic well and are doing a lot in terms of risk assessments and choosing the right materials upfront. Other people don't understand what is actually needed – and they are in danger of potentially large delays in delivering their product to market. Regulators expect sound E&L data."

And the devil, says Feilden, is in the details: "Experiments must be designed such that they can detect complex chemical species at the levels at which they are deemed to be toxic or increase risk. To do that effectively, you need to consider a variety of factors, including instrument capability and sensitivity, the dosing regime, and the amount of material. You also need to consider your choice of solvents for the extraction process."

Needle in a haystack

More companies are focusing on biologics and increasing amounts of plastics (with their inherent potential for leachables) are entering pharma's manufacturing chain thanks to the rise of single-use technologies – and that means the workload of E&L tests is rising. Fortunately, the analytical world is keeping pace by developing new, faster technologies that allow for lower limits of detection, while at the same time simplifying the identification process with software and shared libraries. The end result? Greater confidence in the safety of a drug product – and the right data to appease regulators.

Kyle D'Silva from Thermo Fisher Scientific believes that analytical technology has seen advances in three key areas: performance, confidence and usability. "Leachables are varied and complex chemical species. Being able to identify a potential problem – the needle in the haystack – has demanded analytical advances," he says.

Feilden points to a particular challenge that impacts limits of detection – the differences in potential dose depending on medication. "At one end of the scale, you may have an asthma inhaler that delivers a dose of 50 microliters three or four times, right up to dialysis where the biggest dose I've ever heard of is 75 liters. That's a huge difference in dose," says Feilden. "And from an analytical point of view, that represents a challenge. Can you use the same methodologies and instrumentation for asthma inhalers and dialysis bags? And for inhalers, do we have sufficient analytical capability? Instrumentation is rapidly advancing in this area. But identification of the chemical species is another question altogether."

D'Silva has one answer: "Modern instrumentation allows users to both identify and quantify complex chemical species at very low levels. With Orbitrap-based high

resolution accurate mass (HRAM) mass spectrometry instruments, such as the new Thermo Scientific™ Q Exactive™ GC system, we are able to remove interfering background noise for exceptionally clean spectra and routinely gain mass accuracies of one part per million (ppm). Such a high level of mass accuracy has a real advantage when you're faced with unknown peaks because it increases the confidence in compound identification. Perhaps equally importantly, the systems themselves are also considerably easier to use than they were back in my university days."

In addition to advances in instrumentation, software is also evolving to help interpret data faster, using comprehensive libraries that allow users to cross check data. Currently, libraries tend to be proprietary, but D'Silva expects to see more shared cloud-based libraries in the future, which could simplify E&L analysis. He says, "Tests are being done in labs all over the world all the time – and I think these libraries should be freely available."

Previously, labs tended to be secretive about their findings, but Feilden, who sits on the boards of several industry groups, says that more information is being shared using cloud-based services. Although sharing doesn't eliminate any of the laboratory work – all pharma companies must perform E&L studies – it can at least aid in faster compound identification, so that risks can be eliminated more quickly. D'Silva adds, "I really believe that cloud-based libraries are the future. And we already have some resources available, for example, mzCloud.org, which features a freely searchable collection of high resolution/accurate mass spectra. The database includes several thousand compounds and several hundred E&L leachable impurities. We hope there will be even more in the future."

Knowledge versus ignorance

Perhaps one of the reasons why some people have shown a lack of interest in E&L is that, despite the effort involved in the studies, it doesn't appear to make a 'better' product – instead, says Feilden, "The work leads to a safer product for the patient. All of the work is solely to understand and then reduce risk to an acceptable level."

You might think that all manufacturers want to minimize product risk, but according to D'Silva you'd be surprised at how many companies are reluctant to delve too deeply. "When we demonstrate technology that can confidently identify peaks in a way that wasn't possible before, some people express disappointment because they assume more identified peaks means extra work! We understand (but don't condone) this point of view. However, thanks to advances in software – it actually doesn't mean more work from an analytical perspective. Admittedly, there may be more to do from a risk assessment perspective, but this information is important and will allow for better product understanding and decision making," he explains. "For example, you may see a peak at a very low level in a drug that's been on the shelf for three months, but it could be a dominant peak once the drug has been on the shelf for years. Surely, it's better to be aware of that than to be blissfully ignorant of a potential safety problem?"

"From my point of view, advanced mass spectrometry is becoming essential rather than just 'nice to have'," says Feilden. "The cost of today's new technology has come down to routine level. Sometimes you may look at a price list and think it's too expensive, but when you look at the total cost of analysis, coupled with extra capability and confidence, new systems come out on top. I would go as far as saying that companies that perform E&L testing without the latest equipment may not be around in a few years – after all, it's a competitive market."

"All of that said, there's no silver bullet," he adds. "Even with the best technology and vetted libraries of contributed compounds, no single technique can detect and identify everything."

"Being able to identify a potential problem – the needle in the haystack – has demanded analytical advances."

D'Silva agrees, "E&L (much like any other contaminant analysis) tends to require a multi-faceted approach. Liquid chromatography, gas chromatography, ion chromatography, and a number of different detection platforms might be needed to detect the whole range of potential E&L chemicals. But while I realize there is no single system for all E&L testing, advanced tools that offer increased sensitivity or accuracy or reliability can remove some of the question marks."

Nevertheless, the pharma industry has been slow to adopt such advances. And although legacy instrumentation can 'get the job done', D'Silva says that each E&L peak is associated with a degree of identification uncertainty. "In some ways, it all comes down to how much uncertainty you are willing to accept. If you look at mass spectral libraries that have been on the market since the 1970s, you'll find a few compounds that were misidentified," says D'Silva. "The analysis would have been performed by a very qualified lab, but the technology at the time simply wasn't advanced enough. Today's technology can re-identify those compounds – with greater confidence."

Feilden concludes, "Deciding whether to use the latest available tools really comes down to balancing investment versus the risks associated with potentially dangerous chemical compounds being present – but unseen."