INTERVIEW

Addressing the risk presented by extractables and leachables in cell therapy manufacturing

The identification and measurement of extractables and leachables (E&L) is a critical element of advanced therapy QC. David McCall (Senior Editor, BioInsights) speaks to Jason Creasey (Managing Director, Maven E&L Ltd) about regulators’ expectations and the importance of adopting a risk-based approach to E&L for cell therapy developers.

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Q What are you working on right now?

JC: Right now, I am continuing to run my consultancy business, which is devoted to extractables and leachables (E&L). It allows me to continue working full-time in the area of E&L—a journey that began for me in the mid-1990s. This actually coincided with the beginning of interest in E&L in general, which started in the inhalation space with metered dose inhalers. As well as supporting clients, I also like to find time to present on the topic at conferences and seminars, and I work with the Extractables and Leachables Safety Information Exchange (ELSIE) Consortium as a scientific advisor. So, I guess you could say I am mildly obsessed with the topic!
Why are E&Ls so important to the cell and gene therapy field in particular? What is really ‘need to know’ about them for those working in the space?

**JC:** When it comes to advanced therapies such as cell and gene therapies, E&L should be considered, since it studies and manages a specific risk to the safety and purity of these medicines. Managing the risks to safety or purity of medicine is a key step in every pharmaceutical development program. What changes is the size of the risk for different types of products. For example, products that are delivered by the parenteral route, which is the case for many advanced therapies, are among those that are at higher risk from leachables.

Let me define what is meant by E&L, because I think that is important to understand. Starting with the ‘L’ part, the term ‘leachables’ has been used by the pharmaceutical industry to describe an impurity that enters the drug product formulation as a result of an interaction of that formulation with materials of construction of either the manufacturing process and/or the packaging and delivery device. These systems contain a lot of plastics or elastomers, which can be a source of substances (small molecules) that leach from the materials into the drug product and are then delivered to patients receiving the medicine.

In order to study these leachables, experiments are designed to study this possibility and the specific substances in these materials, because of the risk that leachables may either be toxic to the patient themselves, or may affect the quality of the drug product, which in turn has a negative impact on the patient. These designed experiments are the ‘E’ part. Doing extractable experiments helps in a number of ways. It helps predict what the leachables may be, and it helps you develop your leachable methods of analysis (by defining targets). It is also helpful to know which of your materials of construction are the source of a leachable. This then gives you the choice to replace that material, if the leachable derived from it is a concern.

Earlier in my career, I led a team at GlaxoSmithKline tasked specifically with looking at E&L. One of our major responsibilities was to develop analytical methods to look for extractables in the materials of construction, and methods to look for leachables in the drug product. This was not a trivial task since it is a wide and varied set of substances that may be released from plastics and elastomers, and in many instances, we were uncertain as to what these substances were before we developed and tested the methods of analysis.

The development, validation, and application of such analytical methods is a complex and time-consuming activity, which needs planning and dedication as well as advanced analytical chemistry skills and equipment. That is why the typical model for E&L analysis today is to leverage a mixture of in-house and outsourced resources.

As well as designing and operating the analytical methods, you then have to understand the results and make decisions on whether the risk from leachables is high enough to warrant doing something about it.

Like every drug, advanced therapy products are evaluated and approved by a regulatory authority prior to use, so any information generated must be communicated effectively to that authority. As I have explained, leachables have the potential to affect both the safety and efficacy of a medicine. To determine the associated risk, measurements are made to demonstrate both what is present in the medicine and how much of it might be dosed to patients. In the
case of cell or gene therapies, their methods of manufacture and delivery can increase the risk that leachables affect patients. In many ways, they are unique, because the patient’s cells or genetic material may be placed directly in contact with formulations of the medicine both during manufacture and when the medicine is finally introduced back into the patient. With most other medicines, the leachables are only introduced in that final delivery step.

Q: How and why might the importance of E&Ls increase further as the regulatory environment for advanced therapies continues to evolve and mature?

JC: The regulatory environment has certainly developed over time. For advanced therapies, this area continues to innovate and evolve in an attempt to deliver better and better therapies to patients. This may be through the introduction of novel materials of construction and novel methods of delivery—in principle, both could offer mechanisms for a greater risk from leachables, if risk assessment is not fully considered in their design. Traditional approaches to the evaluation of impurities were based around knowledge of the active pharmaceutical ingredient (API) and its potential impurities, as these were considered the highest risk items. However, regulators are now much more likely to ask companies to consider any element that may offer a risk to patients.

Q: Are there any particular concerns or considerations around divergence in regulatory opinion and guidance relating to E&Ls in the global setting?

JC: I think the concern here is a lack of consistency in expectations. Right now, we do not have universal guidance on E&L. The guidance that does exist can be quite general or indeed contradictory in places. However, there is an ICH guidance document under construction (ICH Q3E) and there is hope that this may lead to a greater consensus of opinion on this area—that would be most welcome. For now, the best advice is to be science-led in justifying the approaches you take to E&L analysis.

Q: What are some of the keys to adopting a risk-based approach to E&L requirements, and what is the optimal timing for planning and then implementing such an approach?

JC: In many ways, the risk-based approaches to E&L are the same as those in use for the other aspects of pharmaceutical development. Unfortunately, though, people do sometimes neglect to use them for this particular area.
The most critical item is probably to employ QbD. Selecting good materials for construction is key to this. There is a concept in pharmaceutical development (outlined in ICH Q8) of creating a quality target product profile (QTPP). This can be extended to the selection and requirements for the materials of construction of both manufacturing equipment and packaging and delivery devices. If you select materials with a knowledge and understanding of their potential to produce leachables then of course, this lowers the risk. That is not always easy to achieve, but I think the attempt is worthwhile.

This QTPP then influences the timing of events. It means that you have to be prepared to consider activities around E&L at three specific points (and to potentially repeat activities, if required). Firstly, as I have implied, there is the design stage. Here, you may be selecting and specifying materials of construction and thus, a period of risk assessment and evaluation might be undertaken. Secondly, you have the period of clinical development leading up to and including regulatory approval of the marketed product. As I mentioned earlier, regulators will expect a package of information that will confirm the risk from leachables is low. Thirdly, there is the lifecycle period, post-approval. During this period, there may be changes made to the approved product and these changes need to be evaluated for their potential to introduce new leachables, or to increase the amount of existing ones.

The studies around E&L are linked to these three stages, and each stage is linked together by a risk management process designed to ensure planned activity is connected to any changes made. This is quite difficult to achieve; you want to conduct studies only when the materials of construction are defined and not subject to change, but of course, those studies need to be completed prior to point where you need to present them for regulatory approval.

What are the key E&L-related analytical tools and assays available today, and what might be coming down the innovation pipeline next?

**JC:** I guess this is one of the reasons I have kept within this area throughout my career. It has always been the case that we have needed to adopt cutting-edge analytical tools to study extractables or leachables. This is because we are frequently asked to perform screening exercises to detect ‘everything’ that may be present in a given material of construction or a drug product formulation. Clearly, ‘everything’ must have some caveats, but it frequently means pushing the limits of analytical science in terms of detection limits and the ability to identify and quantify at the trace level. In order to achieve this, it is now generally agreed that it is appropriate to subdivide the screening into three subgroups of organic substances (volatile, semi-volatile and non-volatile). Whilst there is some overlap, this can be translated into three complementary...
analytical methods—two gas chromatography-based assays (covering volatiles and semi-volatiles) and a liquid chromatography-based assay. Each of these methods is typically coupled with mass spectrometry (MS) to allow detection and identification, although other detectors are sometimes used to support and supplement MS.

Regarding the future pipeline of tools, each of these analytical approaches is subject to almost continual innovation and development, driving either better detection limits or mechanisms of identification. Certainly, over the period of my involvement in the E&L field, MS has developed significantly—for example, the use of higher-resolution MS has allowed for significant improvements in the identification of substances. I think one area linked to this, which still needs further development, is our ability to transform the large quantities of raw output into meaningful results and knowledge. It is now quite possible to collect vast amounts of data, but the attempt to successfully interpret and transform that into useful knowledge has only just begun.

**Q** You have been actively involved with a variety of initiatives, groups, and publications aimed at developing best practices relating to E&Ls—can you pick out any particular conclusions or directions from these activities that you would like to see regulatory bodies acting upon or adopting in future?

**JC:** I have been very lucky to be involved in a large number of initiatives relating to E&L over the last two decades. I was involved in the review of the original 2006 PQRI OINDP recommendations for E&L, and it is interesting to see how this document has influenced the direction of E&L ever since. Arguably, its most important achievement was to set a safety-based risk threshold for leachable study, and then link it to the analytical method requirements. Prior to this document, researchers were forced to use the instrumental detection limits as a guide for how low to detect leachables. I think this principle of linking analytical requirement to a knowledge-led risk assessment of leachables is still very important, the most important part being the risk-based aspect. We are still sometimes held back by not conducting our assessments of leachables based around the risk they pose. Determining the risk is not always easy, but it is something I think we can do. Very often, the absolute true risk from a leachable is low—however, we struggle to demonstrate this because we lack certainty in the information available to us. There is uncertainty in the analytical measurements made, and there is uncertainty in the safety assessments conducted due to lack of information on toxicity. Therefore, I would ask that regulatory authorities do all they can to facilitate the collection and circulation of tools and information that work to reduce this uncertainty.

**Q** Finally, can you highlight one or two key goals and priorities that you have for your work over the foreseeable future?

**JC:** My goal is to continue to aid in reducing the uncertainty I have mentioned. Right now, there are lots of different groups spending resources conducting analysis on their drug
products for leachables. This is a time-consuming and potentially expensive activity. One of the ways in which I think I can help is to bring groups together in areas of joint benefit. I don't believe this is an area where there is anything to be gained from not collaborating for best effect. Many of the systems used are common throughout the industry and I think that at the moment, there seems to be a lot of repetition in the testing being done by different groups. If we can move to a position of better agreement both on what is required to be done, and on what is an effective means to then share and disseminate risk outcomes, perhaps this area can move forward more rapidly. As a field, we can then focus on areas of true risk while wasting less time on low-risk situations.

BIOGRAPHY

JASON CREASEY is a graduate analytical chemist. In 2019, he established Maven E&L Ltd, as its Managing Director and Principal Consultant. Maven E&L was setup to provide advice to clients working in the pharmaceutical industry on all aspects relating to the topic of extractables and leachables (E&L) and the risks that leachables pose to the quality and safety of drug products. Prior to this, he worked for GlaxoSmithKline, where he was the director of their R&D E&L Team. He has worked in the topic area of E&L since the mid 1990s on a wide range of modalities and dose forms seeing this area expand and grow in significance for the pharmaceutical and medical device industries. In addition to running his consultancy, he is a scientific advisor to the ELSIE consortium. Since setting up Maven E&L; he continues to present, discuss, and write about E&L. He now publishes a regular E&L blog through LinkedIn and his website (www.MavenEandL.com), for the exchange of ideas and discussion. As well as supporting client projects, among recent E&L activity, he is presenting and commenting on risk-based approaches to E&L requirements within the pharmaceutical industry, that he hopes will form part of an ICH guidance in the not-too-distant future, and has helped ELSIE publish and discuss their white papers linked to concepts in leachable risk management and develop their database further.

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