EXTRACTABLES/LEACHABLES TESTING CONSIDERATIONS FOR SINGLE-USE SYSTEMS

Here, Sandi Schaible, Senior Director of Analytical Chemistry and Regulatory Toxicology at WuXi AppTec, discusses testing considerations for extractables and leachables along with the regulatory environment for single-use systems.

Traditionally, drugs are manufactured in large stainless-steel containers. These containers pose two main hurdles to drug manufacturers. First, the stainless-steel systems have to be thoroughly cleaned after each batch, with testing required to ensure that the container is free of contaminants. While such containers are reusable, the cleaning process requires significant time and resources. Furthermore, because the containers are made of stainless steel, manufacturers do not have the flexibility to change the size of the drug batch on a case-by-case basis.

Single-use systems (SUSs) eliminate the need for arduous cleaning processes and validation testing. Moreover, they can also allow for scaling batch sizes, require a much smaller footprint in the manufacturing facility and reduce cost.

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DESIGNING EXTRACTABLES SCANS IN THE ABSENCE OF REGULATORY REQUIREMENTS

Regulatory requirements have yet to catch up to the rising use of SUSs, however. Most regulatory bodies ask to see extractables/leachables (E/L) data as a part of the submission process, but there is not a uniform requirement for how that testing should be done or what it should include. China already requires E/L testing for SUSs. Likewise, the EMA and International Council on Harmonization have begun to expect E/L testing data for SUSs.

In the absence of formal regulations, the BioPhorum Operations Group (BPOG) published the first standardised extractables protocol in 2014. The BPOG protocol, as it is commonly referred to, is based on the extraction capabilities of various solvents over recommended time periods. That protocol was revised in 2020, removing some extraction solvents and paring down the extraction timepoints.

The US Pharmacopeia (USP) recently issued two new chapters (665/1665) on production equipment and patient safety for polymeric components and systems used in biomanufacturing. The new USP chapters provide information for assessing risk and a standardised testing procedure. USP <665> discusses the characterisation of plastic components and systems used to manufacture biopharmaceutical drug substances and biopharmaceutical and pharmaceutical drug products. USP <1665> discusses the selection and qualifications of plastic components and systems used to manufacture APIs, biopharmaceutical drug substances and biopharmaceutical and pharmaceutical drug products.

Even though E/L studies on SUSs are not explicitly required by regulatory bodies, they are still essential for drug development and safety/toxicological risk assessments. Moreover, the new USP chapters also give regulatory bodies a test method to point

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to as they request the data they would like to see. In the absence of clear guidance for E/L studies on SUSs, the following section covers some factors to consider regarding study design.

DETERMINING WHICH SUS COMPONENT TO TEST

It is not the expectation that every component in a SUS needs to be tested. There are multiple methods to determine which components should be tested. When evaluating which SUS components to test, careful consideration should be given to how the SUS will interact with the final drug product. Factors to consider include:

- **Proximity to the final drug product:** When SUSs are used upstream in the manufacturing process, there may be opportunities for leachables to be filtered out or diluted downstream in the final drug product and thus may not be considered a high risk for leachables. However, SUSs used downstream may have a much higher risk of the leachables reaching the final product.
- **Contact duration:** Extractables study design should also factor in the amount of time that the drug product is in contact with the SUS component. Longer durations can result in more opportunities for leachables to migrate out and at a higher concentration.
- **Temperature:** Higher temperatures during the manufacturing process should be considered when evaluating if a SUS component might be at higher risk. These conditions can create more opportunities for leachables to release from the plastic of the SUS and into the final drug product.
- **Contact surface area:** The greater the surface area of the SUS that is in contact with the drug product, the more opportunity for leachables to make their way into the final drug product.
- **Type of plastic:** Most single-use plastics are made from several materials. That said, softer plastics generally have more potential for leachables in greater quantities than more rigid plastics.

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CONSIDER CLINICAL USE CASE

A drug product's clinical use is also an important consideration for E/L testing. For example, final drug products that are used for neonates are more likely to have a much lower permitted daily exposure for leachable chemical compounds than ones used in adults.

Frequency of use also matters. A drug that will only be used once may have a higher threshold for leachables than a drug that will be administered on a daily basis for a prolonged period of time. Toxicologists must consider the potential for leachables to accumulate in a patient's body.

The potential benefit of the drug product versus the potential risk should also be considered. In some cases, such as a drug developed in response to a public health emergency or to treat a rare disease, a higher threshold may be tolerated because of the potential benefit of the drug.

COMPLETE CHEMICAL CHARACTERISATION IS CRITICAL

In the absence of comprehensive regulatory requirements, complete chemical characterisation is still an essential part of the process because of the role it plays in a safety assessment/toxicological risk assessment. Complete E/L testing identifies all chemicals within a SUS. Unidentified chemicals must be considered carcinogenic or genotoxic; therefore, when unknowns are present, it is virtually impossible for the toxicologist to accurately assess safety or risk. Simply put, unknowns are unacceptable.

Given the way the regulatory environment is evolving, manufacturers should consider laboratory testing partners that offer a commitment to complete chemical characterisation as a default for extractables scans, have an existing database of compounds and expert scientists who can identify new compounds.

A FINAL WORD

SUSs are rising in popularity for drug manufacturers, but regulatory bodies have not kept pace with definitive requirements for E/L testing. In the absence of such guidance, drug manufacturers should still conduct robust testing, striving for complete chemical identification and characterisation.

ABOUT THE COMPANY

As a global company with operations across Asia, Europe and North America, WuXi AppTec provides a broad portfolio of R&D and manufacturing services that enables the global pharmaceutical and healthcare industry to advance discoveries and deliver groundbreaking treatments to patients. Through its unique business models, WuXi AppTec's integrated, end-to-end services include chemistry and drug development contract research, development and manufacturing organisation (CRDMO) services, biology discovery, preclinical testing and clinical research services, cell and gene therapies contract testing, development and manufacturing organisation (CTDMO) services, helping customers improve the productivity of advancing healthcare products through cost-effective and efficient solutions. WuXi AppTec received an AA environmental, social and governance (ESG) rating from MSCI in 2021, and its open-access platform is enabling more than 5,800 collaborators from over 30 countries to improve the company's health of those in need, and to realise the company's vision that "every drug can be made and every disease can be treated".

ABOUT THE AUTHOR

Sandi Schaible is the Senior Director of Analytical Chemistry and Regulatory Toxicology at WuXi AppTec, located in St Paul, MN, specialising in extractables and leachables studies. She is a US delegate and international delegate for ISO 10993 part 18 in chemical characterisation, and also a US delegate for ISO 10993 part 13 and the particulates committee (TIR42).