The Landscape for Single-Use Systems

Single-use systems hold enormous potential in the pharma manufacturing industry, reducing cost, start-up times, and improving risk evaluation of extractables and leachables

Single-use technology, often described as single-use systems (SUS) or single-use equipment, has the potential to transform pharmaceutical manufacturing by offering tremendous opportunities to reduce cost, improve flexibility or cycle time, and shorten the time needed to build a manufacturing process for new, life-saving drugs. Their adoption offers numerous advantages for greater efficiency and productivity in applications such as final filtration, mixing, and aseptic connections. SUS can reduce capital investment in facilities and equipment, eliminate the need for cleaning procedures and their required validation, reduce start-up times, and decrease the risk of cross-contamination.

However, this success is very much dependent on how effectively the industry approaches the development and implementation of single-use technology. Ultimately, a new drug can only be successful if it is effective, safe, and available. Traditionally, only a comprehensive understanding of the drug product and manufacturing process can achieve these goals. This remains true as SUS is introduced in place of traditional reusable equipment. Encouraging an open science and risk-based dialogue during supplier audits and evaluation of SUS supply chains significantly improves SUS implementation (1).

Despite these advantages, SUS can also contain risks. Key challenges facing the developers and end users of single-use bioprocessing technologies include their limited scale, the restricted diversity of options, and some remaining performance issues that can be addressed by further R&D (2). As with most disruptive technologies, there is an absence of standardisation and regulation of the quality of materials used. Polymeric materials in SUS can introduce a range of unwanted chemicals into the manufacturing process fluid. For patient safety, biomanufacturers must systematically assess and mitigate the risks posed by any extractables and leachables (E&L) in these systems. Unfortunately, the burden of assessing and mitigating any identified risk based on E&L data is the top reason some researchers restrict their use of SUS. One of the key reasons cited by manufacturers for not taking up disposable technologies is the lack of a validation process to determine the nature, quantity, and risk associated with E&L from the disposable plastics, which could potentially contaminate product intermediates (2).

General Regulatory and Industry Expectations

The general guidelines for both the FDA and EU GMP discuss that materials that come in contact with the drug product must not be reactive, additive, or absorptive as to affect the quality and efficacy of the drug (3-4). PDA Technical Report 66, which is for the application of SUS, includes examples of collecting supplier quality certificates and test results with their reference standards as part of the evaluation of supplier quality (1). The updated USP <661.1> focuses on the material of construction of the main plastic components used in the pharma industry, including requirements for biological reactivity testing, chemical testing, and its subsequent acceptance criteria based on each type of material (5). Biological reactivity as discussed in USP <661.1> and ISO 10993 for medical devices should be performed in accordance with USP <87> and <88> (6-7).

Regulatory Expectations for E&L Evaluation

Although formal guidelines for E&L assessments have not yet been enacted, there is nonetheless a regulatory expectation that researchers will test for these potentially harmful contaminants. Agencies such as the FDA's Center for Biologics Evaluation and Research recommend a risk-based approach to evaluation. In such an approach, indication, safety, product characteristics, dosage, formulation, and stability are all factors. If the process is lower risk, the sponsor can submit supplier data for certain materials and demonstration of lower risk without additional testing. If there is relevant risk, the sponsor may have to determine toxicity based on maximum dosage of potential leachables derived from extractables data. If the risk of maximum dosage of potential leachables remains, leachable evaluation and testing may be necessary. Furthermore, if product quality could be affected by a potential leachable, studies may need to assess the effect on product quality, including efficacy. These evaluations are possible when the supplier provides extractables data, which can supplement final product quality assessments.

Beyond the regulatory sphere, numerous industry organisations have created best practice strategies for implementing extractables studies.

As discussed, the purpose of evaluating E&L is to demonstrate patient safety with respect to the identity and quantity of potential leachables in the final drug product and their potential toxicity to patients. The purpose is not to test every material that comes in contact with the product during the manufacturing process, but to evaluate the risk and perform extractables testing based on the risk assessment. The risk assessments published by both BPOG and USP <1665> draft evaluates criteria including temperature and duration of contact, chemical nature of the process stream, materials of construction, and distance to the final drug product/clearance steps (8-9). If, based on the extractables evaluation, a risk to the patient still exists, then mitigation including leachables testing may be needed.

The use of simulation studies and less aggressive extractables studies are better at predicting potential leachables without the interference of the drug product matrix. Performing leachables testing on a drug product itself will add additional cost as it would be product-specific and could potentially interfere with the evaluation of compounds. Choosing model solvents that bracket the drug product as a simulated worst-case will result in compounds that are the most likely potential leachables. Being in a clean matrix allows for better detection and quantitation of the results. Concerns around using model solvents that are too aggressive, such as a 0.5N sodium hydroxide solvent for a product that has a pH of less than 10, could result in a worst-case patient safety evaluation and lead to unnecessary additional evaluation and testing, especially if the component's compatibility with the solvent is a concern (10).

Although there is a chance that a leachables compound may not be identifiable, the compound class and similarly structured compounds would be present in an extractables analysis. The resulting safety assessment with slightly higher concentration and similar compounds will have a worst-case evaluation of potential leachables that is much more conservative than evaluating leachables. Therefore, if safety can be demonstrated from extractables, subsequent leachables testing does not need to be performed unless the concentration of the potential leachables still demonstrates a risk.

Future Expectation and Other Considerations

Advancements in complex pharmaceutical drugs such as monoclonal antibodies (mAbs) and cell and gene therapy drugs are leading to questions concerning the effect of SUS on the performance of the cell culture, oxidation of the protein, or interaction with the cell. The generation of E&L is affected not only by the materials of construction, but the sterilisation method. Linking these potential leachables to product quality and efficacy of the drug is difficult. It is more important to identify the material and sterilisation method and link to efficacy and product stability concerns. Creating a risk-based approach and testing for stability concerns earlier in the process will be important when designing single-use assemblies.

Aligning the recommendation from compendial standards, industry and community groups will be essential to eliminating confusion, setting a minimum standard, and leveraging existing data. Using a risk-based approach with the understanding of risk reduction with embedded mitigation steps such as tangential flow filtration can reduce risk, while focusing on downstream processing and final fill as the highest risk (11). The draft of USP <665> is the first compendial method that focuses on extractables analysis on systems used in the manufacturing of pharmaceutical drug products, and updates to the extractables evaluation guidance from BioPhorum Operations Group gives confidence that the SUS industry is moving closer to alignment. Risk evaluation of E&L and ensuring patient safety is important. Establishing appropriate expectation will help ensure that life-saving drugs reach patients when they need them.

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Jessica Shea is responsible for Extractables and Leachables Global Technical Support at **MilliporeSigma**. Previously, she was the Manager of the E&L laboratory for the BioReliance® Validation Services. She has more than 12 years of E&L experience, including method validation, designing of custom testing, and interpreting industry and regulatory guidance.

jessica.shea@milliporesigma.com