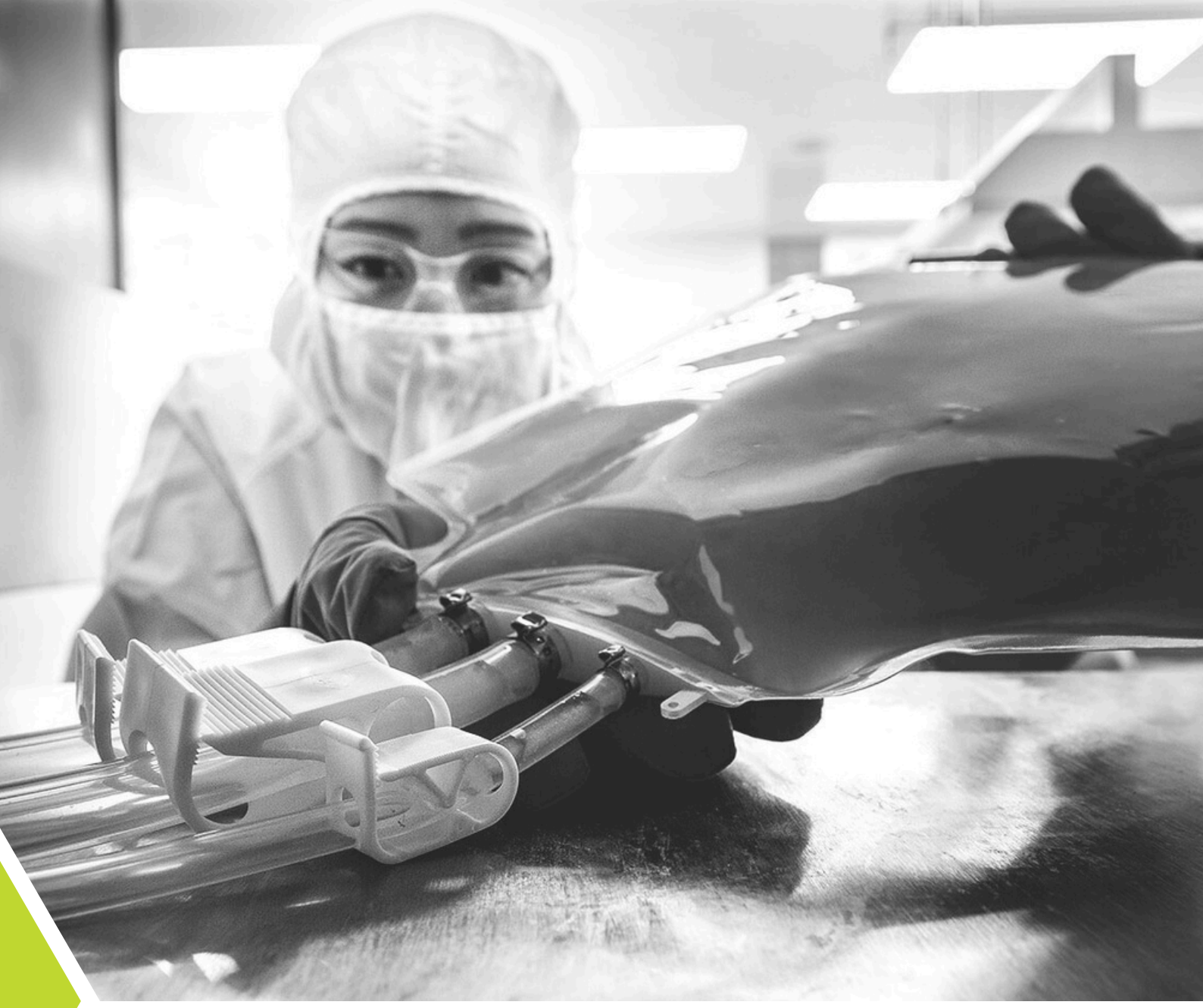


Understanding and Implementing **USP <665>** for Single-Use Systems

White Paper

solvias

Executive Summary

In the dynamic landscape of pharmaceutical and biopharmaceutical manufacturing, single-use systems (SUS) have revolutionized processes by offering flexibility, efficiency, and cost-effectiveness. However, ensuring the safety and quality of pharmaceuticals manufactured using SUS requires rigorous testing and adherence to industry standards.

The United States Pharmacopeia (USP) Chapter <665> "Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products" provides crucial guidance on the analytical testing of SUS to mitigate the risks associated with extractables and leachables (E&L). Chemically characterizing and qualifying plastic components used in manufacturing is certainly an inevitable task. Mandatory compliance with USP Chapter <665> is expected as it will become official on May 01, 2026. Therefore, it is imperative for manufacturers to begin preparing now to ensure full compliance and avoid any disruptions when the new standards come into effect.

Understanding USP <665>

USP <665> provides a thorough explanation of the potential E&L complications from implementing single-use components in a manufacturing process as follows. During the manufacturing process, the process stream, production intermediates, drug substance (DS), or the drug product (DP) itself may directly encounter and thus, potentially interact with, one or more plastic components of the manufacturing system. During this contact, substances could leach from a manufacturing component and become incorporated into the process stream. If these substances persist in the process stream through subsequent process operations, they could accumulate in either a DS or DP as process equipment-related leachables (PERLs). If they are present in the DP, PERLs have the potential to alter critical quality attributes of the DP, such as safety, efficacy, and stability. Some examples of these substances that could become potential PERLs include: antioxidants, degradation products, pigments, plasticizers, lubricants, mold & slip agents, stabilizers, and monomers.

The standardized extraction protocol described within USP <665> is designed to explore the potential of these compounds to be leached. Briefly, the chapter provides for general chemistry testing of low-risk components, which leads to organic extractables profiling with a single extraction solvent for medium-risk components and expands to three extraction solvents for higher-risk situations. The protocol, based upon the utility of a 50% alcohol solution, attempts to cover most commonly encountered process situations. Essentially, establishing baseline testing for a “representative case”, not a “worst case” scenario. Obviously, pH and polarity can also be examined, as well as any extracted elements.As with all extractables and leachables studies, the goal of the study is to generate data which can help establish that the components selected are suitable for their intended use.

Scope

- Tubing and connectors used for fluid transfer and transport
- Bags, bioreactors, liners, impellers, and container ports used in mixing, reacting, and fermenting
- Storage containers for raw materials, production reagents, and process intermediates
- Filters and chromatography columns used in processing
- Filling needles/devices
- O-rings, gaskets, check valves, septa, diaphragms, polymer pump surfaces, and sensors, and other ancillary components

Risk Assessment in USP <665> Compliance

Risk assessment is a cornerstone of USP <665> compliance. It involves a systematic evaluation of the potential risks associated with extractables and leachables (E&L) from single-use systems (SUS) in the context of a specific manufacturing process. This assessment considers various factors, including the nature of the SUS components, the process stream, contact conditions (e.g., temperature, duration), purification processes, and the risk profile of the drug product itself. By conducting a thorough risk assessment, manufacturers can identify the most critical SUS components and process parameters that warrant closer scrutiny. This allows for targeted testing and mitigation strategies, ensuring resources are allocated efficiently and effectively.

THE RISK ASSESSMENT PROCESS TYPICALLY INVOLVES:

Component Identification
Identifying all SUS components that come into contact with the drug substance, drug product, or their intermediates.

Material Characterization
Gathering information about the materials of construction of the SUS components, including their chemical composition, manufacturing processes, and potential degradation pathways.

Process Mapping
Mapping the entire manufacturing process to identify all potential points of contact between the drug substance/product and SUS components. Establishing conditions of use and chemical properties of the process stream, including duration and temperature.

Risk Identification
Identifying potential sources of extractables and leachables, considering both the inherent properties of the materials and the process conditions. Remembering to consider the nature of the dosage form as well as the dosage.

Risk Evaluation
Evaluating the potential severity of the identified risks based on the toxicity of the extractables/leachables, the patient population, and the route of administration or clinical use/duration of the drug product. Minding the ability of the purification process operations to eliminate or dilute the PERL(s) to such an extent that an adverse effect is unlikely.

Risk Control
Implementing appropriate risk control measures, such as selecting SUS components with lower risk profiles, optimizing process conditions, or incorporating additional purification steps.

Preparing for the USP Deadline

The official date for USP compliance has been extended to **May 1, 2026**. To ensure a smooth transition, pharmaceutical and biopharmaceutical manufacturers should:

1. **Review USP <665> Requirements**
   Familiarize themselves with the latest version of USP <665> and understand the specific testing requirements for their products.
2. **Identify Single-Use Components and Systems**
   Conduct a thorough inventory of all SUS used in their manufacturing processes.
3. **Develop a Testing Plan**
   Create a comprehensive testing plan that outlines the specific tests to be performed, the acceptance criteria if applicable, and the timeline for completion.
4. **Select a Qualified Testing Laboratory**
   Partner with a reputable laboratory that has experience in USP <665> testing and possesses the necessary expertise and equipment.
5. **Conduct Testing**
   Implement the testing plan, ensuring that all tests are conducted in accordance with USP requirements and industry best practices.
6. **Review Results and Ensure Compliance**
   Thoroughly review the test results and compare them against expectations. If any concerns are observed, take appropriate corrective actions, including seeking out toxicological input.
7. **Maintain Documentation**
   Maintain comprehensive documentation of all testing activities, including test plans, protocols, results, and any follow up actions taken.

Complying with USP <665> is not a one-time event but an ongoing process that requires continuous vigilance. As the pharmaceutical industry evolves and new technologies emerge, the landscape of SUS and E&L risks is constantly changing. Manufacturers must stay informed about the latest regulatory developments, scientific advancements, and industry best practices to ensure their compliance programs remain effective and up to date. As manufacturing processes change, new SUS components are introduced, or new information about E&L risks becomes available, risk assessments should be updated accordingly. Collaboration between manufacturers, SUS suppliers, testing laboratories, and regulatory authorities is essential to fostering a culture of continuous improvement and ensuring the safety of pharmaceutical products. By sharing knowledge and best practices, stakeholders can collectively work towards mitigating risks, advancing analytical technologies, and strengthening the regulatory framework.

Streamlining USP <665> Compliance

Navigating the complexities of USP and E&L testing can be a daunting task for pharmaceutical and biopharmaceutical manufacturers alike. Partnering with Solvias can streamline the compliance process. By partnering with us, you can benefit from:

Reduced Time and Cost
Our streamlined processes and efficient workflows help you save time and resources.

Expertise
Our scientists have extensive knowledge of USP requirements and testing methods.

State-of-the-art Equipment
We utilize advanced analytical instruments to deliver accurate and reliable results.

Comprehensive Services
We address all aspects of USP <665>, providing a one-stop solution for our clients.

Our comprehensive suite of services includes access our two Centers of Excellence for Extractables and Leachables, one in the US and one in Switzerland. With over twenty years of experience with polymeric and elastomeric materials used in container-closure systems, packaging systems, and single-use systems, we specialize in trace organic analysis, screening, development, and validation services utilizing mass spectrometry.

Canton, MA - United States

- ✓ >2,000m² of lab space
- ✓ 9 FDA inspections and multiple DEA inspections
- ✓ Over 20 client audits annually
- ✓ Controlled substance license for schedules 1–5

Kaiseraugst - Switzerland

- ✓ >12,500m² facility
- ✓ Inspected by FDA (most recent Sep ‘23) and Swissmedic
- ✓ Over 100 client audits annually
- ✓ Infrastructure for scheduled and highly potent substances

We employ a wide range of analytical techniques to identify and quantify E&L compounds, including:

- Direct injection and headspace-sampling gas chromatography-mass spectrometry (GC-MS), gas chromatography-tandem mass spectrometry (GC-MS/MS) and gas chromatography-orbitrap mass spectrometry (GC-HRAM-Orbi) for the determination of volatile and semi-volatile compounds.
- Liquid chromatography-mass spectrometry (LC-MS), Liquid chromatography-tandem mass spectrometry (LC-MS/MS), liquid chromatography-quantitative time-of-flight mass spectrometry (LC-HRAM-QToF), Liquid chromatography-orbitrap mass spectrometry (LC-HRAM-Orbi) for the determination of non-volatile compounds.
- Inductively coupled plasma-optical emission spectrometry (ICP-OES) and Inductively coupled plasma-mass spectrometry (ICP-MS) for elemental determinations.

Looking Ahead

USP-NF comprises a dynamic series of standards that are continuously evolving to keep pace with advancements in pharmaceutical and biopharmaceutical manufacturing and analytical technologies. Efforts are underway to develop standardized protocols for E&L testing to ensure consistency and comparability of results across laboratories. The upcoming revisions are expected to further strengthen the standard's requirements for E&L testing, emphasizing the importance of risk assessment and ensuring the safety and efficacy of pharmaceutical and biopharmaceutical products. By staying abreast of the latest developments in USP monographs and partnering with experts such as Solvias, manufacturers can proactively manage risks, ensure compliance, and safeguard the quality of their products.

Emerging Trends in USP

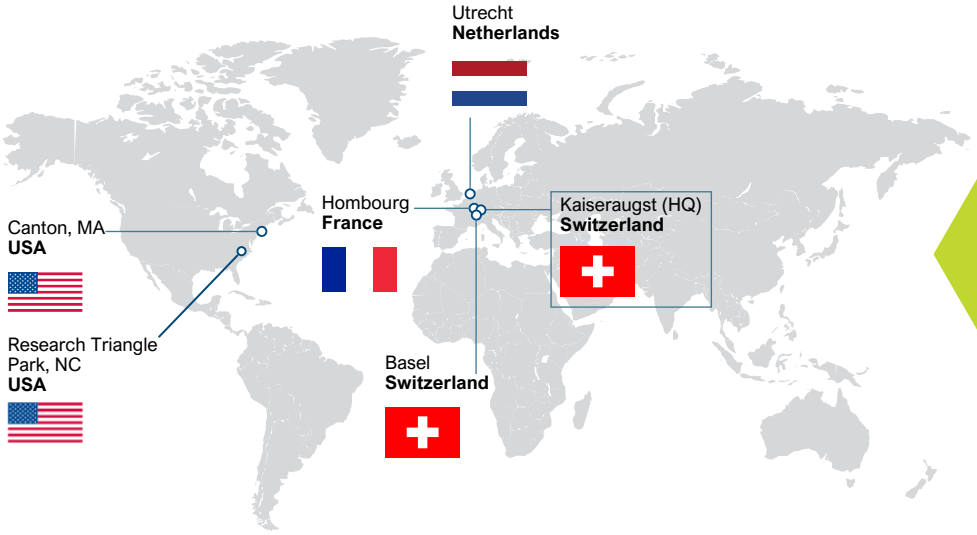
- **Increased Focus on Leachables:** There is a growing emphasis on leachables testing as it provides a more realistic assessment of the potential risks associated with E&L. New chapters following <1664.1> are under consideration for other routes of administration.
- **Adoption of New Analytical Techniques:** Advancements in analytical techniques, such as high-resolution accurate mass spectrometry (HRAM), are being adopted to enhance the sensitivity and selectivity of E&L testing. HRAM is a true “must-have” for structural elucidation of any unknown impurities. This technology is a focal point of Solvias’ offerings.
- **Development of Standardized Protocols:** Solvias is at the forefront of these emerging trends, participating in industry work groups, continuously investing in new technologies, and expanding our capabilities to provide our clients with the most advanced and comprehensive services available.

Conclusion

USP <665> plays a critical role in ensuring the safety and quality of pharmaceuticals and biopharmaceuticals manufactured using single-use systems. By complying with this standard, manufacturers can mitigate risks, enhance product quality, meet regulatory requirements, and strengthen their brand reputation. Solvias is committed to supporting pharmaceutical and biopharmaceutical manufacturers in achieving these goals by providing comprehensive, high-quality, and timely USP <665> testing services. We are your trusted partner in navigating the complexities of E&L testing and ensuring the success of your products. For further information and details about these analytical testing services, or to get in touch with an expert, contact us at **info@solvias.com**.

Why partner with us?

- CDMO/CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 22.5K sqm of lab capacity
- 700+ customers worldwide
- 6 centers of excellence



Contact us to speak with an expert: info@solvias.com

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