



USP <665>
Transparency
Sterilization
Process Readiness
Risk Assessment

Safety and Sterilization Guidelines For Single-Use Technologies

METTLER

TOLEDO

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USP <665> for Single-Use Technologies in Biopharmaceuticals

Single-use technologies are essential in contemporary biopharmaceutical manufacturing, offering flexible production, quicker changeovers, and reduced contamination risks in both upstream and downstream processes. The U.S. Pharmacopeia (USP) provides important guidelines for assessing single-use sensors, particularly regarding USP <665> readiness and risk management. USP <665> sets standardized criteria for extractables and leachables (E&L) to minimize contamination of drug products caused by Process Equipment-Related Leachables (PERLs), thereby ensuring the safety and quality of pharmaceutical products throughout the manufacturing process.

USP <665> became effective on May 1, 2026, and following its implementation, compliance will be required for all applicable manufacturing systems and components. This standard specifically applies to plastic components and systems used in the manufacture of various pharmaceutical products, including all manufactured drug products (DPs), pharmaceutical drug products, biopharmaceutical drug substances, and manufactured drug substances (DSs).

USP <665> applies to plastic components and systems used in the manufacture of:

- All manufactured DPs
- Pharmaceutical drug products
- Biopharmaceutical drug substances
- It is also applicable to manufactured DSs

This may include:

- Single-use assemblies
- Tubing
- Connectors
- Sensor systems
- Mixing and bioreactor components

Single-use sensors (SUS) are becoming integral components in biopharmaceutical manufacturing, embedded directly into bioreactors, mixing systems, filtration assemblies, media preparation systems, sampling manifolds, and fill-finish workflows. These sensors frequently come into direct or indirect contact with critical process streams, necessitating thorough evaluation of their material composition, fluid-contact surfaces, adhesives, encapsulants, gamma stability, sterilization compatibility, potential extractables, and long-term interaction with the process. As a result, sensor technologies have become integral components of the overall process contact system, playing a critical role in ensuring safety, reliability, and efficiency in biopharmaceutical production.

1. USP <665> and Material Transparency

Material transparency is a critical consideration in the use of SUS for biopharmaceutical manufacturing. Manufacturers increasingly demand detailed documentation covering polymer composition, fluid-contact materials, manufacturing controls, sterilization methods, and supplier change management.

The materials used in SUS are essential for ensuring product safety, efficacy, and compliance. They must be compatible with the biological substances processed and must not leach or contaminate the final product. SUS manufacturers must provide information on material qualification and suitability, following regulatory requirements outlined in guidelines such as the EU GMP Guide Part II, 21 CFR 211.65(a), and ICH Q7A.

It is essential to ensure that interactions such as extractables, leachables, adsorption, and by-products do not compromise the quality of the pharmaceutical product. While regulatory requirements primarily address the final product rather than the entire biotechnological process, compliance with pharmacopeial guidelines remains critical. USP <665> provides comprehensive guidelines for materials used in biopharmaceutical manufacturing, helping to ensure their safety and suitability. Pharmaceutical manufacturers hold the ultimate responsibility for demonstrating that selected single-use sensor (SUS) materials consistently produce products of defined quality under specific process conditions.

2. USP <665> and Gamma Sterilization Compatibility

The compatibility of single-use components with gamma sterilization is essential for the safety and effectiveness of biopharmaceuticals.

Gamma sterilization uses high-energy gamma rays to eliminate microorganisms. It is widely recognized by regulatory bodies as a process that destroys all life forms, including fungi, bacteria, viruses, spores, and endotoxins. Many single-use assemblies are gamma-irradiated before use.

Post-sterilization, sensors must maintain measurement stability, mechanical integrity, calibration consistency, and signal reliability. Potential issues include polymer degradation, signal drift, optical instability, membrane alterations, and adhesive failure. Manufacturers should confirm that suppliers have validated sensor performance under sterilization conditions that mimic actual use.

3. USP <665> and Calibration and Process Readiness

Calibration of single-use components is vital for ensuring accuracy, reliability, and regulatory compliance in biopharmaceutical manufacturing.

Calibration involves comparing sensor readings to known standards, making necessary adjustments, and documenting results to maintain traceability and support audits. Proper calibration is a fundamental aspect of Good Manufacturing Practice (GMP) and is crucial for maintaining product integrity and successful pharmaceutical operations.

Drug manufacturers should choose sensors that offer simplified deployment, stable pre-calibration, rapid process readiness, reduced setup complexity, and consistent batch-to-batch performance. Reducing operational complexity enhances manufacturing agility and facility utilization. Operational efficiency is increasingly crucial in large-scale single-use manufacturing. Complex recalibration can cause startup delays, increase operator intervention, reduce batch transition efficiency, and add validation burdens. However, single-use instruments often lack full traceability and cannot be factory-calibrated as complete units, unlike reusable systems.

4. USP <665> and Integration into Risk Assessments

USP <665> supports a risk-based evaluation model for single-use sensors, considering factors such as process exposure conditions, drug sensitivity, contact duration, temperature, solvent exposure, sterilization conditions, and flow path criticality. Each application has a unique risk profile, and collaborative supplier documentation along with application-specific assessments help streamline qualification and ensure regulatory compliance.

Key elements include identifying suitable materials through risk assessments, focusing on extractables and leachables (E&L) with standardized data for patient safety, and reviewing documentation according to ICH Q9 guidance for efficient evaluations.

Implementing USP <665> enhances risk management and guides permissible exposure levels. Maintaining system integrity through sterility and leak-free processing is also critical. These factors collectively enable manufacturers to demonstrate control over single-use systems via documented testing, compatibility studies, and validated procedures. With increasing use of single-use technology in high-risk aseptic processes such as final sterile filtration, thorough risk evaluation is essential to ensure patient safety and manage new complexities effectively.

5. Supplier Support and Documentation

Successful implementation of single-use systems often depends on the responsiveness and technical support provided by suppliers. Effective collaboration ensures that potential issues are addressed promptly, enabling smoother integration and operation within manufacturing processes.

Suppliers are expected to provide critical documentation to support both technical deployment and regulatory compliance. This includes material declarations, extractables reports, gamma validation studies, shelf-life data, quality certificates and certifications, change notifications, and validation support packages.

As a result, manufacturers increasingly prefer suppliers who not only deliver reliable products but also offer robust technical support and thorough compliance documentation. This dual capability facilitates efficient qualification, risk management, and ongoing validation efforts, ultimately contributing to successful product implementation and regulatory confidence.

The growing adoption of single-use technologies in fluid-contact environments, coupled with accelerated therapy scale-up and heightened regulatory demands, underscores the need for reliable, compatible single-use sensors. These sensors are vital for ensuring operational agility, compliance, and consistent outcomes in biopharmaceutical manufacturing.

USP <665> is reshaping how manufacturers evaluate single-use process systems, including integrated sensing technologies. Beyond regulatory compliance, manufacturers are increasingly prioritizing operational simplicity, faster deployment, supplier transparency, risk reduction, and process consistency. As single-use manufacturing continues to evolve, sensors that support both process performance and compliance readiness will play an increasingly vital role in scalable biopharmaceutical production.

6. METTLER TOLEDO Pendotech Solutions

METTLER TOLEDO Pendotech offers advanced single-use sensor solutions designed to meet the stringent requirements of USP <665> for biopharmaceutical manufacturing. These sensors are engineered to ensure compliance with the latest regulatory guidelines by providing thorough risk-based evaluations that consider critical factors such as material compatibility, sterilization stability, extractables and leachables, and fluid-contact safety. With a focus on gamma sterilization compatibility, METTLER TOLEDO Pendotech sensors maintain calibration accuracy, mechanical integrity, and signal reliability even after irradiation, supporting rapid process readiness and reducing operational complexity. Supported by robust supplier documentation—including material declarations, extractables data, gamma validation, and calibration records—METTLER TOLEDO Pendotech sensors aid manufacturers in streamlining qualification, enhancing risk management, and demonstrating regulatory compliance. By addressing the growing demands of accelerated therapy scale-up and expanded regulatory expectations, METTLER TOLEDO Pendotech's single-use sensors contribute significantly to operational agility, process consistency, and scalable biopharmaceutical production.

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