PALL Biotech

Extractables and Leachables

Ready for USP <665>?

Document Number:	RPSCEL_01
Revision Number:	1.0
Date:	27-Nov-2019
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Contents

1 What Are USP <665> and <1665>?

On March 1, 2019, the United States Pharmacopeia (USP) published a third draft of chapters <665> and <1665> establishing minimum requirements for fluid-contact, plastic components, and systems used in the manufacturing of pharmaceutical drug substances and products. Whereas the <665> chapter establishes standardized extraction conditions and test requirements for plastic components, which are likely to be enforced by regulators, the high level (>1000) level <1665> chapter provides additional guidance information to facilitate implementation of <665>. The expectation is that manufacturers of plastic components used in cGMP pharmaceutical manufacturing will generate extractables data in compliance with USP <665> and make these data available to end users to aide in component selection and qualification.

Based on public feedback and comments shared by the USP packaging expert committee, there will likely be a final revision of USP <665> and <1665> published in the USP Pharmacopoeia Forum in early 2020. The key requirements for compound-specific component testing are expected to remain unchanged in the revision. What is expected to change is that topics related to materials testing and treatment of silicone components, will likely move to a different or future USP chapter.

2 What Are the Benefits of USP <665>?

Implementation of USP <665> will support the International Conference on Harmonisation principles: (ICH) Q8 and Q8 (Pharmaceutical Development and Quality by Design [QbD]), and Q9 (Quality Risk Management [QRM]). The intent is to ensure baseline, well-understood (i.e standardized) physicochemical characterization packages are available for all fluid-contact, plastic components used in pharmaceutical drug manufacturing, and that these datasets are available to end users early in the component selection and drug development processes. In addition, other potential benefits to industry may include, but not necessarily limited to, a reduction in testing costs by eliminating the need for repetitive testing by end users; and minimizing risks related to the appearance of unexpected compounds. Moreover USP <665> establishes a common industry language amongst key stakeholders, including: regulators, end users, integrators, component manufacturers, and material suppliers for the minimum level of information expected for plastic equipment used in drug manufacturing. This is done in a manner that enables a quick and cost-effective way to risk assess fluid-contact materials associated with highly configured single-use systems, and compounds likely to impact critical quality attributes of the drug product.

3 What Types of Test Data Will Be Required by USP <665>?

USP <665> recommends a risk-based approach, where the minimum level of testing is commensurate with the expected risk. All components should meet the *low risk* testing requirements including reporting of non-volatile residue (NVR), UV absorbance, and delta pH shift values of 50% ethanol/water extracts. For *medium risk* components, additional, compound-specific extractables profiling of the 50% ethanol/water extract is performed, which typically includes testing by headspace GC/MS, direct injection GC/MS, and LC/UV/MS for volatiles, semi-volatiles, and non-volatile compounds. Components deemed high risk, are expected to meet the low and medium risk requirements, plus additional compound-specific organic extractables profiling in a low pH (pH 3), and high pH (pH 10) solution; as well as testing for elemental impurities.

Table 1.

Risk Level	Biological Reactivity Tests	Extraction Solution for Chemical Testing	Chemical Testing of Extracts
Low	(No testing)	✓ 1/1 (v/v) ethanol/water	✓ Non-volatile residue ✓ UV absorbance ✓ Delta pH
Medium	✓ USP<87> Cytotoxicity tests	✓ 1/1 (v/v) ethanol/water	✓ Low-risk tests (above) ✓ Organic extractables profiling
High	✓ USP<87> Cytotoxicity tests ✓ USP<88> Systemic injection test	✓ Acidic solution, pH 3 ✓ 1/1 (v/v) ethanol/water ✓ Basic solution, pH 10	✓ Low-risk tests (50% EtOH/water) ✓ Extractables elements ✓ Organic extractables profiling

4 How Can a Component Manufacturer Know the Application Risk?

In the biotech marketplace, it is impossible for a manufacturer to understand every conceivable application in which their component may be used. However, there is a general understanding of typical application conditions for which the component is expected to be supported. For example, depth filters are most commonly used immediately downstream of cell harvest regarded as low risk applications, whereas sterilizing grade filters and biocontainers are frequently used in high risk downstream formulation and filling applications. Of course, other components such as o-rings and tubing may be used in a variety of ways throughout the manufacturing process, and this is where the beauty of suppliers providing clearly-identified low, medium, or high-risk datasets ensures baseline data are available and properly aide in a QbD component selection process.

5 How Is USP <665> Different from USP <661>?

Historically, many suppliers have employed USP <661> for physicochemical characterization of plastic components, which included pass/fail metrics for NVR, UV absorbance, and pH shift measurements in water extracts. However, with recent revisions to USP <661>, these historic test requirements have been withdrawn from <661> and replaced by <661.1> requirements for polymers used in packaging, <661.2> requirements for container closures, and the proposed USP <665> for plastic components used in pharmaceutical processing. Although the <665> *low risk* requirements share many similarities to historic <661> testing (i.e. NVR, UV, pH shift), the <665> preparation conditions, solvent, and timepoints are unique and thus require retesting to comply with <665>.

5.1 Do I Also Need USP <661.1> or USP <661.2>?

USP <665> advocates a QbD approach, whereby manufacturers of polymeric components will select raw polymeric materials that meet the requirements of USP <661.1>. This offers key benefits such as an understanding of how, and from what raw materials, compounds identified in the <665> extraction profile originate. In addition, this approach encourages component manufacturers to engage with raw material suppliers who are committed to supporting materials for the biotech

market. However, in terms of requirements for plastic components used in pharmaceutical manufacturing, <665> specifically states that when a component's compliance with <665> specifications has been established, material testing (i.e. <661.1>) is established to be non-essential testing. Hence, there is no requirement for components already meeting the requirements of <665> to have their individual materials of construction back-tested per the testing specifications of <661.1>.

USP <661.2> defines requirements for plastic packaging systems for pharmaceutical drug products, and requires an appropriate chemical safety assessment including extractables testing of the packaging system and leachables assessment of the packages drug product, consistent with USP <1663> and <1664>. As Pall Biotech components and single-use systems are intended to enable drug manufacturing of drug substances and drug products, as opposed to final packaging of drug product, Pall Biotech components are tested to meet the requirements of USP <665>.

6 Does Pall BPOG Extractables Data Cover the Requirements of <665>?

Although there is now strong alignment and overlap between the November 2014 BioPhorum Operations Group (BPOG) extractables protocol and USP <665> requirements, current language in USP <665> indicates limited additional testing is required to fully comply with USP <665>. This additional testing includes the USP <665> low risk, non-specific testing requirements such as NVR, pH shift, and UV-absorbance, and in some cases, the pH 10 organic extraction profile for a single timepoint. In applications where the process contact fluid is greater than the USP <665> pH 10 extraction solvent, then USP <665> allows the BPOG high pH solvent, 0.5 N NaOH, to be substituted for the USP <665> pH 10 solvent. However, if the pH of the process fluid is less than or equal to pH 10, then current language in <665> requires a pH 10 extraction solvent profile. Pall Biotech's component testing approach includes the pH 10 conditions so as to cover the both USP <665> and BPOG end user requirements.

7 When Will USP <665> Start to Be Enforced?

The earliest USP <665> is expected to become an enforceable requirement is 2025. However, given the withdrawal of the traditional USP <661> physicochemical testing standard, the expectation is that <665> compliance will almost immediately become the de facto baseline expectation, well before 2025.

8 Are All Plastic Components *in Scope* of USP <665>?

USP <665> covers fluid-contact, plastic components used for drug substances (with exclusions) and drug products associated with 'traditional' pharmaceuticals, 'small molecule' drug products, biopharmaceuticals and vaccines. It applies to both single-use systems as well as multi-use systems. USP does not cover applications for active pharmaceutical ingredients (APIs), non-fluid contact components, or auxiliary items, such as scoops, funnels, pipettes, graduated cylinders or weighing dishes.

9 Will Pall Biotech Provide USP <665> as Well as BPOG Reports?

Pall Biotech is fully committed to ensuring end users have available USP <665> data for components manufactured by Pall Biotech and is working closely with our supplier network to ensure <665> compliant datasets become available for integrated components not manufactured by Pall (e.g. tubing, sensors, fittings). We expect these data to be available well before 2025, which is the earliest USP <665> is expected to become an enforceable requirement. In addition, Pall Biotech continues to generate BPOG extractables data in order to best support Pall components and facilitate extractables risk assessments for end users.

To see the current list of available USP <665> and BPOG extractables datasets on Pall Biotech-manufactured components, please go to https://biotech.pall.com/en/regulatory.html

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