USP<665> FREQUENTLY ASKED QUESTIONS

How much time do I have before I am out of compliance with the roll-out of USP<665> in May 2026?

Once USP <665> is officially effective (May 2026), it is considered in effect immediately for products/packaging systems within its scope—unless your specific customer quality agreement, contract, or an internal change-control/implementation plan defines a phased approach.

In practice, the "time to comply" is usually driven by:

- Your customer's expectations (many will require compliance at/near the effective date, especially for new qualifications).
- Whether you're addressing new systems vs. legacy systems already in use (legacy often handled via risk-based justification and staged requalification).
- Your ability to support compliance via extractables characterization and/or controlled material change aligned to <665>/<1665>.

How do I know if I need to perform this test on my product?

> Is your product a "polymeric component" used in manufacturing a drug/biologic?

USP <665> applies to plastic/polymeric materials and components (e.g., tubing, bags, connectors, manifolds, filters housings, gaskets, bottles, carboys) that contact process fluids used to manufacture drug substances/drug products.

If your product is not polymeric or never contacts product/process fluid, <665> is typically not applicable.

> Is it used in a regulated application where the user will claim USP alignment?

Even if USP <665> isn't legally "mandatory," it often becomes required because end users reference USP in their filing/validation and will flow requirements down to suppliers via specifications/quality agreements.

> Where in the lifecycle are you? (new vs. legacy vs. change)

- New component / new material / new supplier / major design change: expect to need an extractables assessment consistent with <665>/<1665>.
- Existing (legacy) component with no changes: you may be able to justify via risk assessment plus existing extractables/leachables data plus comparability, then test only where gaps exist.

What is my Risk Level?

USP<665> provides guidance into evaluating specific Risk Levels for different products and applications, as a rule of thumb:

- High risk if: direct contact and any two of (high temp/long time, aggressive fluids, high SA/V, gamma/SIP/CIP).
- Medium risk if: direct contact but mostly mild conditions (buffers/WFI, moderate time, limited sterilization).
- Low risk if: no product contact, or only brief contact under mild conditions with low SA/V and no harsh sterilization.

What is the difference between Low, Moderate, and High Risk testing?

Testing	Low	Moderate	High
Extraction Solvent(s)	Organic - Ethanol	Organic - Ethanol	Organic - Ethanol Acidic - Phosporic Acid Caustic - Sodium Hydroxide
Extraction Times	Typically, lower (24 hours) but depends on the product	Typically, lower (24 hours) but depends on the product and may be as long as 21 days	May require several extraction time intervals (varies from 24 hours to 21 days)
Analytical Techniques	UV-Vis NVR	LC-MS/MS GC-MS/MS	LC-MS/MS GC-MS/MS ICP-MS

Does your laboratory support custom Chemical Compatibility / extraction conditions?

Yes! Contact our Laboratory for more information on how we may support your custom extraction conditions or perform a tailored Chemical Compatibility study to meet your needs.

How will I know if my product passes or fails?

>For USP <665>, "pass/fail" is usually not a single yes/no test result. It's typically a decision based on:

- Was the extractables study executed per the agreed protocol (conditions, methods, QA, documentation)?
- Do identified extractables remain below toxicological thresholds for the intended use?
- Are there any red-flag compounds (e.g., known genotoxins, nitrosamine risks, certain catalysts) requiring mitigation?
- Is the profile consistent lot-to-lot / change-to-change (comparability)?

>In practice, acceptance is defined by one (or a combination) of these:

- Analytical Evaluation Threshold (AET) approach: compounds above AET must be identified/quantified; then a tox assessment determines acceptability.
- Customer specification: customer may define explicit limits (e.g., metals limits, specific compounds not detected, total organics limits).
- Comparability to a qualified baseline: new lot/material change must be "no worse than" the qualified extractables profile within defined criteria.

>So you "pass" when:

- The extractables profile is characterized to required thresholds and
- Toxicological risk assessment concludes acceptable patient safety margin for the intended dose/exposure and
- Any customer-specific requirements are met.

>You "fail" (or require remediation) when:

- Extractables exceed thresholds and cannot be justified toxicologically, or
- A prohibited/high-concern compound is present, or
- The profile changes materially vs the qualified baseline without acceptable rationale.

Do I need to perform the whole package?

No, the validation requirements are largely determined by regulatory bodies and end users. It is advised to consult with your customers and compliance contacts to ensure the validation package is tailored to your needs.

Tell me more about:

Filterability: provides customers with a measure of how well their filtration process will perform in the final filtration. There are various techniques employed to accomplish this as well as various computational methods that are utilized to interpret the results. May utilize either a pump or pressure vessel to achieve either Vmax or Pmax calculations and can be performed utilizing filter discs and/or cartridges/capsules.

Challenge Organism Viability: before any bacterial retention challenge can be conducted, a viability study must be carried out to ensure that the sample does not have a detrimental effect on the viability of the bacterial challenge organism (or surrogate fluid).

Product Wet Integrity Test Values: performed to establish the DF and BP integrity test values of the filter product after defined exposure to customer product. Reference values for integrity testing filters in customer product solution will be established and scaled to any size of the same filter type.

Filter Compatibility: a method that conditions the filter product(s) under customer product process conditions to check for filter and production process compatibility via the maintenance of integrity post exposure in order to verify sterilizing grade performance is maintained.

Bacterial Retention Challenge: this test is performed to validate that a filter can remove bacteria from a gas or solution, usually using a standard organism such as B. diminuta to challenge the filter performance. The goal is to demonstrate that the filtration process will consistently remove high levels of a standard bacterium or relevant bioburden isolate, suspended within the product (or surrogate fluid), under typical process conditions.

Extractables & Leachables: sterilizing grade membrane filter cartridges and devices are used to remove bacteria and particulate from pharmaceutical preparations. It has been shown that the liquid can have a significant effect on the performance of the materials used in the construction of the filter and lead to low levels of extractable and leachables being present in the filtered product. For filter validation packages, the standard method of analyzing the presence of these contaminants is non-volatile residue (NVR) analysis.

CONTACT INFORMATION:

Parker Hannifin Corporation
Bioscience & Water Filtration Division
2340 Eastman Avenue
Oxnard, CA 93030

phone +1 877 784 2234
bwf.oxn.support@parker.com

www.parker.com/bioscience