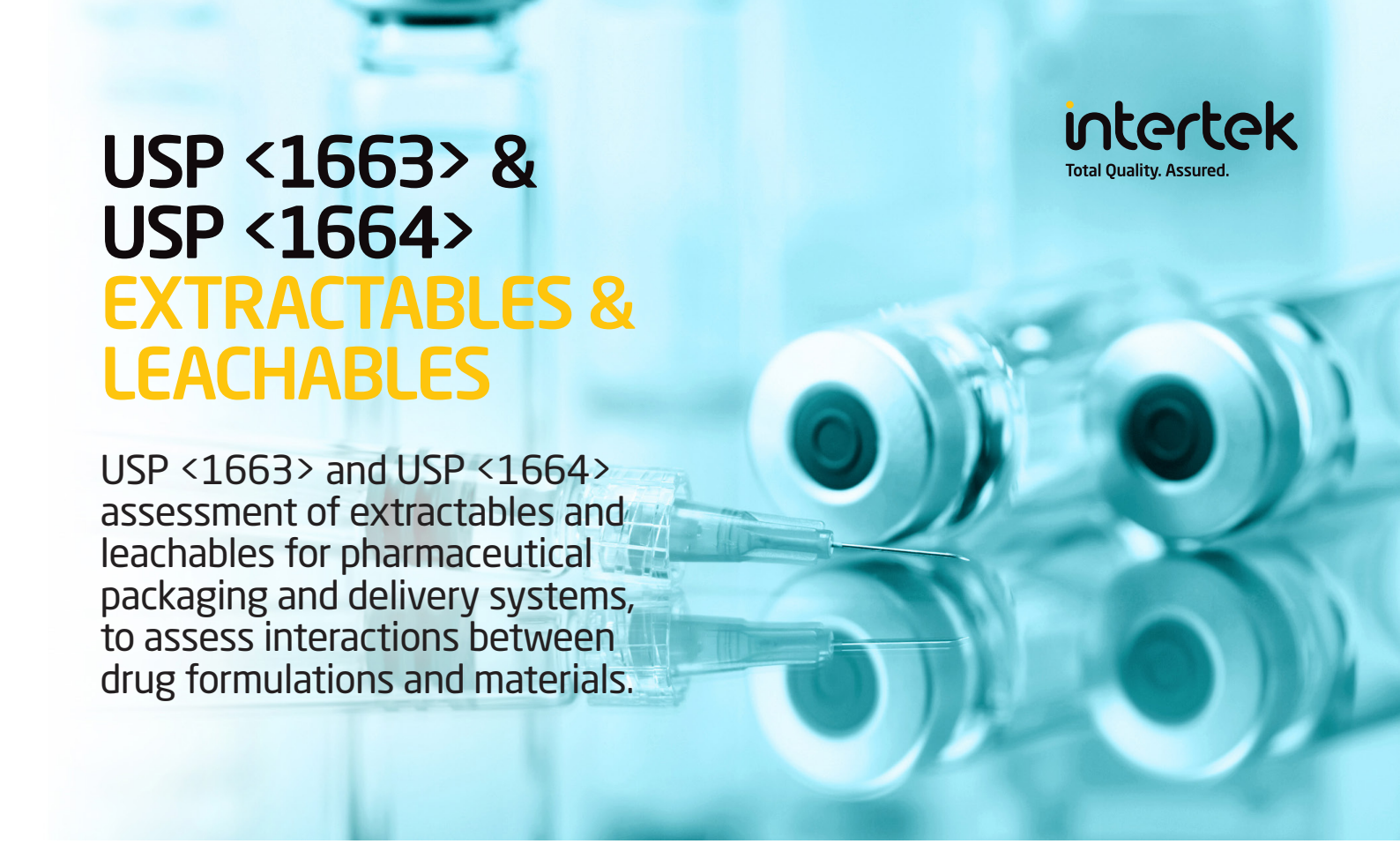
USP <1663> & USP <1664> EXTRACTABLES & LEACHABLES



USP <1663> and USP <1664> assessment of extractables and leachables for pharmaceutical packaging and delivery systems, to assess interactions between drug formulations and materials.

Guidelines such as USP <1663> and USP <1664> are key documents governing extractables testing and assessment of leachables, ensuring the safety of pharmaceutical packaging and delivery systems. This requires rigorous assessment of potential interactions between drug formulations and the materials used in packaging. By identifying and quantifying potentially harmful substances that can migrate from packaging materials into drug products, manufacturers can mitigate risks associated with product contamination, stability issues, and patient safety concerns.

USP <1663> - Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

USP chapter <1663> addresses the evaluation of extractables associated with pharmaceutical packaging and delivery systems. Extractables are substances that can migrate from packaging materials under stressed conditions, such as exposure to solvents or elevated temperatures. The purpose of USP <1663> testing is to identify these substances, build an extractables profile and assess their potential impact on the quality, safety, and efficacy of the drug product.

Key Points of USP <1663>

Definition and Scope: Extractables are substances that can migrate from packaging materials into the drug product under artificial stress conditions. USP <1663> places particular emphasis on the chemical properties of the drug formulation, such as the fact that many drug products are compositionally intermediate between polar and non-polar, as well as the route of administration.

Testing Procedure: The testing replicates conditions that simulate potential interactions between the drug product and packaging materials. This includes using solvents and elevated temperatures to extract substances that may leach into the drug product over time. Extraction processes should be timely but not so aggressive that they alter the extractables profile by e.g., damaging the packaging. The most aggressive conditions are used for quantifying chemical additives in components. These studies aim to measure specific known additives, not simulate a leachables profile, so using extraction conditions that disrupt the component or material is acceptable.

Various solvents and harsh conditions are also used to determine the extraction profile of the complete packaging and the device. The aim is to extract more from the packaging than would be the case during the maximum storage period (slightly exceeding the "worst case"). For this reason, the solvents should exceed the extraction properties of the formulation, but the extraction should not deteriorate the material to obtain still a realistic profile, which is later correlated with the leachables.

In addition to worst case extractables studies, a leachables simulation study which is typically performed directly on aged drug formulation, or a suitable surrogate, can help to assess the detected extractables in a more realistic way to narrow down to the relevant potential leachables. The simulation study is performed under milder clinical use conditions and mostly it is performed as a screening to cover different compound classes – which is like the worst case extractables study. It also helps to better understand the impact of the formulation on the extractables profile even reaction products of formulation ingredients and extractables could be detected this way.

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Toxicological Assessment: Extracted substances undergo toxicological evaluation to determine their potential risk to patients.
Extractables assessments can help:

- Characterize packaging/delivery systems, components, and materials of construction
- Aid in developing safe dosage form packaging/delivery systems by selecting suitable components and materials
- Evaluate the impact of manufacturing processes (e.g., sterilization) on packaging components and potential leachables
- Establish worst-case leachables profiles to facilitate leachables studies, specifications, and safety evaluations
- Assess patient exposure to chemicals from direct contact with packaging or medical device components
- Establish qualitative and quantitative leachables-extractables correlations
- Develop extractables specifications and acceptance criteria for packaging components and materials
- Investigate the origins of leachables causing quality or safety issues in marketed products

USP <1664> - Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery Systems

USP <1664> focuses on the assessment of leachables, which are substances that migrate from packaging materials into the drug product under normal conditions of use, potentially affecting its stability and safety. Unlike extractables, leachables testing involves assessing the long-term impact of these substances on drug product quality and patient safety. Note, this chapter does not define acceptable standards for leachable levels.

USP <1664> Testing: Unlike extractables testing, leachables testing involves longer-term exposure studies to cover real-world conditions. The study on leachables is a target component analysis carried out under real storage conditions on real stability samples at different points in time. The relevant leachables are determined from the data of the extraction and simulation study. This should include all species that are expected to be present in a real sample at a later stage and are potentially problematic for the patient. The leachables study should also use methods that enable the screening of unknown leachables, as long-term storage may well result in new leachables that were not visible in the previous extraction or simulation study. The analytical methods are validated for the target components in the formulation and the specifications are defined. Samples with different shelf storage times are then analyzed for leachables. If previously unknown leachable substances are found, these must also be reported and, if necessary, toxicologically evaluated. Like the extractables studies the leachables study should involve multiple analytical methods to cover different compound classes and polarities.

Extractables Leachables Testing in Accordance with USP <1663> and USP <1664>

At Intertek, we specialize in comprehensive E&L testing services aligned with USP <1663> and <1664> chapters. Our state-of-the-art facilities and experienced team enable us to conduct thorough assessments that meet regulatory requirements and ensure product safety.
We offer:

- **Method Development and Validation:** Tailored testing methods to suit specific pharmaceutical packaging systems
- **Toxicological Assessments:** Evaluation of extracted and leached substances to assess potential risks to patient safety
- **Compliance Assurance:** Adherence to cGMP standards and FDA guidelines to support regulatory submissions

Bringing quality and safety to life, our experts have over 30 years of experience in specialized analytical and toxicology assessment for extractables leachables testing delivered from GMP-compliant laboratories. Our scientists are ready to support you in meeting the requirements of USP <1663> and USP <1664> - contact us now to find out more.

FOR MORE INFORMATION

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Tino Otte, Managing Director at Intertek Switzerland, is an expert for extractables-leachables-studies. He holds a degree in polymerchemistry from the University of Halle/Saale and a Ph.D. from the Darmstadt Technical University, where he graduated in 2010. He joined Intertek Switzerland in 2016. Prior to joining Intertek, he worked with different research, development and manufacturing companies where he served in several functions in product management and development of analytical services. He has many years of experience in GMP regulated environment within multiple areas of product analysis, including method development, validation, and QC.