Drug Development & Delivery

Analytical Testing

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Analytical Testing: New ICH Guideline Outlines E&L Principles

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Earlier this month, the International Council for Harmonization (ICH) released a draft Q3E guideline that offers a harmonized framework for assessing and controlling extractables and leachables (E&L) in pharmaceuticals and biological products. The guideline addresses chemical and biological products, including drug-device combination products. It also considers all dosage forms, factoring in extracting or leaching conditions, the route of administration, the drug's indication, and patient exposure. The guideline proposes a set of risk management principles for assessing the presence of E&L in pharmaceuticals, and outlines a core set of chemical testing and assessment principles for E&L.[1]

The guideline aims to address a gap in the treatment of E&L issues, which are not covered by ICH. ICH states that this gap "generates uncertainty for industry and regulators due to lack of clarity regarding E&L to meet regulatory expectations. The uncertainty creates potential delays in the approval of regulatory applications, and it can lead to variable interpretation."[1]

Additionally, ICH claims that the guideline provides a "holistic framework" for assessing and controlling leachable impurities and expands the existing ICH guidelines on impurities, including impurities in new drug substances (ICH Q3A), new drug products (ICH Q3B), residual solvents (ICH Q3C), and elemental impurities (ICH Q3D), as well as DNA reactive impurities (ICH M7).[1]

Due to the complexities of E&L testing, the global E&L testing services market is expected to jump from $1.29 billion this year to $4.6 billion by 2034.[2] In this exclusive *Drug Development & Delivery* ebook, Stevanato Group discusses E&L from the perspective of lyophilized products, common E&L testing challenges, how to mitigate testing risks.

References

1. ICH releases Q3E guideline on controlling extractables and leachables in drugs, Regulatory News, Aug. 7, 2025.
2. Extractable and Leachable Testing Services Market Size, Shares and Regional Growth, Towards Healthcare, May 21, 2025.

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Extractable and Leachable Challenges in Lyophilized Drug Products

By: Alan Xu, Product Manager, Analytical Services at Stevanato Group, and Piet Christiaens, Scientific Director at Nelson Labs Europe

Lyophilization (lyo) involves removing water from liquid pharmaceutical formulations using a freeze-drying process resulting in a lightweight powder that has a longer shelf life and can be stored at higher temperatures (e.g. room temperature). Despite its benefits, lyo also introduces its own risks related to extractables and leachables (E&L), where the container and drug may interact over time. Therefore, the container, drug, and lyophilization process should be carefully studied to determine the appropriate regulatory and analytical testing requirements.

Container packaging

Primary packaging materials, including glass vials and rubber stoppers, are integral to maintaining the stability of lyophilized drug products. However, these materials can release volatile and semi-volatile compounds, such as through outgassing, which accumulate on the highly absorbent surfaces of the lyo power. Secondary packaging systems, such as multilayer films and aluminum pouches, may also contribute to E&L risks during temperature and humidity fluctuations. These interactions necessitate rigorous testing and method validation to mitigate potential contamination and ensure the product's long-term stability.

Significance of Extractables and Leachables

Extractables are chemical entities that can be released from packaging materials under elevated conditions such as exposure to concentrated solvents or elevated temperatures. Leachables are substances that migrate into the drug product under standard storage or usage conditions.

Regulatory References

Both the United States Food and Drug Administration (FDA) and United States Pharmacopeia (USP) <1664>, categorize product interaction risk or leachables risk based on the dosage form and administration route. For lyophilized drugs (powders for injection/reconstitution), the leachables risk during solid-state storage is considered low but the reconstitution process with liquid can elevate these risks depending on formulation excipients, pH, and overall contact time.

The European Medicines Agency (EMA)'s guidelines includes a decision-tree approach for assessing packaging interactions. For drugs intended for parenteral administration, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use considerations (ICH) recommends long-term stability studies and accelerated testing to identify cumulative leachables over the product’s lifecycle.

Testing Challenges

A major limitation in E&L testing for lyophilized products is the challenge of establishing a true blank solution. Because the lyophilization process inherently involves packaging contact, alternative approaches, such as time-point zero baselines, must be employed. However, these methods are imperfect and introduce uncertainties in distinguishing between inherent impurities and leachables. Advanced analytical techniques, including high-sensitivity liquid chromatography–mass spectrometry (LC–MS) and gas chromatography–MS (GC–MS), are indispensable but require significant expertise and resources to implement effectively.

Mitigating E&L risks

Utilizing low-alkali glass and high-quality, low-residual rubber stoppers can significantly reduce chemical contamination. Proactive collaboration with suppliers during material selection and validation helps ensure compatibility with the lyophilized drug product.

E&L studies must encompass both extractables and leachables testing under simulated real-world and worst-case scenarios. This includes rigorous assessments during storage, reconstitution, and administration. Accelerated testing techniques can enhance study efficiency and provide robust data earlier when selecting the container materials.

Innovative packaging designs, such as non-contact systems and reduced headspace configurations, minimize the accumulation of leachables. Coated or laminated materials further reduce the migration of harmful compounds, improving product safety.

Developing standardized methodologies across the pharmaceutical industry also ensures consistency, improves compliance, and facilitates data sharing. Such protocols should be considered throughout the lifecycle of lyophilized products, from manufacturing to patient administration.

Post-market surveillance programs and ongoing reviews of packaging materials and processes are also essential for adapting to emerging risks and regulatory changes. Pharmaceutical companies can leverage feedback from real-world usage to help collaborate with container manufacturers and analytical laboratories to proactively identify and address vulnerabilities.

Conclusion

The unique process involved in lyophilized drug products results in unique E&L risks. These challenges arise from complex interactions between the drug product and its packaging during storage, reconstitution, and administration. Addressing these risks requires a multidisciplinary approach involving advanced material science, rigorous testing methodologies, and compliance with global regulatory standards. Collaborations such as that between Stevanato Group and Nelson Labs Europe demonstrate how combining expertise in packaging technologies and analytical science can support the development of robust, compliant, and patient-safe solutions

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Selecting the right primary container for an injectable drug or **passing a device design verification test** are crucial steps in the product development process.

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We can cover a range of specialized fields including container closure systems and drug-delivery devices with the goal of assisting our customers to anticipate future challenges and help them navigate the regulatory landscape.

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