

PHARMSOL NEWS Ensuring Product Safety - Extractable and Leachable Studies for Injectable Products

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Adhesives and inks from labels migrating through the \rightarrow lavers of a bag

The most important extractables and leachable for common packaging materials is tabulated below

Packaging Material	Potential Extractable	Potential Leachable	Common Dosage Forms
Glass	Heavy metals (e.g., lead, aluminum), silicates	Boron, sodium,	Parenteral, ophthalmic
Polyethylene (PE)	Plasticizers, hydrocarbons,	Plasticizers (e.g., phthalates), solvents	Oral solids, liquids,
Polypropylene (PP)	Polyolefins, stabilizers	Residual monomers, plasticizers	Oral solids, liquids, parenterals
Polyvinyl Chloride (PVC)	Vinyl chloride stabilizers (e.g., cadmium)	Plasticizers, solvents	Parenterals, IV bags, blood bags
Elastomers (Rubber)	Plasticizers, antioxidants,	Latex proteins, bisphenol A	Prefilled syringes, injectable vials
Aluminum	Heavy metals, organic residues	Aluminum salts, lubricants	Oral liquids, injectable vials
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The significance of E&L Studies in Injectable **Products**

1. Patient Safety: Substances that leach from packaging materials can potentially cause toxicity, allergic reactions, or impact drug efficacy.

2. Regulatory Compliance: Regulatory bodies like the FDA, EMA, and ICH require manufacturers to conduct E&L testing to meet safety standards for injectable products. These tests help ensure compliance with strict guidelines, especially when dealing with products intended for vulnerable populations, such as neonates \Rightarrow or immuno-compromised patients.

3. Product Integrity: E&L substances may degrade or alter the composition of a drug, affecting its stability and effectiveness.

For biologics and vaccines, even small quantities of leachable can change the drug's chemical structure, leading to compromised efficacy or stability.

4. Long-Term Storage: Injectable drugs often have extended shelf lives. Packaging materials must be rigorously tested to ensure that no harmful leachable migrate into the drug formulation during prolonged storage periods.

How Are E&L Studies Conducted?

- Material Selection: The first step in E&L testing involves identifying all components that may come into contact with the injectable product, such as containers, stoppers, syringes, and other delivery devices.
- · Simulated Conditions: The testing is typically done under simulated conditions that accelerate the potential release of substances from packaging materials. This may involve exposing the materials to high temperatures, light, or prolonged contact with the drug product.
- Analytical Testing: Advanced testing methods such as High-Performance Liquid Chromatography (HPLC), Mass Spectrometry (MS), ICP-MS and Gas Chromatography (GC) are used to detect and quantify leachable and extractables. These techniques provide the sensitivity needed to detect even trace amounts of contaminants.
- Risk Assessment: The results of the tests are compared to established safety thresholds, helping to evaluate the risk that any detected substances may pose to patient health.

Challenges for E & L testing

some key challenges include

- Complexity of Analytical Techniques (GC-MS, LC-MS, ICP-MS etc.,)
- Variability in Extraction Conditions- (temperature, solvent type, duration, and surface area to volume ratio)
- \Rightarrow Regulatory Compliancedistinct regulatory requirements as per markets



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Introduction

In the pharmaceutical industry, the safety, quality, and efficacy of injectable products are paramount. Injectable medications, including biologics, vaccines, require rigorous testing to ensure that they meet the highest quality standards. One of the most critical yet often overlooked aspects of injectable drug safety is the Extractable and Leachable (E&L) studies.

E&L studies assess the potential migration of harmful substances from packaging components—such as rubber stoppers, plastic syringes, and container closure systems into the injectable drug product. In this writeup , we will explore the importance of E&L studies, the regulatory framework surrounding them.

What Are Extractables and Leachable?

Extractables refer to substances that are released from materials (e.g., plastic or rubber) when exposed to solvents or pharmaceutical formulations under stress conditions like high temperatures or prolonged exposure. These may include

- Plasticizers from plastic containers. \Rightarrow
- \Rightarrow
- \Rightarrow Degradation of products of polymeric materials.
- Metal catalysts from manufacturing equipment. \Rightarrow
- Additives and process chemicals. \Rightarrow
- Antioxidants used in packaging materials. \Rightarrow

Leachable are substances that migrate from packaging materials into drug formulation over time, particularly during storage or use. These may include

- \Rightarrow The same substances identified as extractables, but under normal conditions.
- \Rightarrow Impurities that can migrate through a directcontact laver.

Dyes or inks from labels or packaging.

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- Identification of Unknown Compounds \Rightarrow
- \Rightarrow Higher cost of Testing (require outsourcing)
- \Rightarrow Longer Test Duration (weeks to months)
- \Rightarrow Material Variability
- \Rightarrow Environmental Factors to simulate testing conditions
- \Rightarrow Sourcing of Materials from various sources
- \rightarrow Risk of Non-Compliance- leads to product recalls, regulatory fines

Conclusion

Extractables and leachable studies play a pivotal role in ensuring the safety, efficacy, and stability of injectable drugs. Critical importance of these tests in identifying potential risks posed by packaging materials and drug delivery systems. Without these studies, patients may experience serious adverse effects, and manufacturers could face regulatory challenges, product recalls, and reputational damage.

The future of E&L testing will likely continue to focus on innovative materials and sustainable packaging solutions while maintaining rigorous safety standards for drug products. By investing in robust testing and adhering to regulatory guidelines, manufacturers can mitigate risks and ensure that their injectable products are both safe and effective.

How PharmSol Helps

- Development and Technology Transfer of simple and **Complex Injectable Products**
- Execution of Bioequivalence Studies for complex injectables as per regulatory requirements
- End to End services for Compilation of Dossier and **Regulatory Filing**
- EUGMP inspections for Sterile dosage forms