

Extractables & Leachables – Regulatory Perspectives

S. P. Manek

Extractables

- *Extractables* are chemical species / compounds that can be extracted from a primary container or component material (*e.g. the elastomeric or plastic components*) into drug or biological product & contaminate and/or cause various potential issues .
- Extractables are mostly generated by interaction between products and their packaging over time, usually under extreme conditions *e.g. the presence of strong solvents or elevated temperatures* .

Leachables

- *Leachables* are compounds that leach into the drug or biological product from the container-closure system - *such as the elastomeric or plastic components, or coatings of the container and closure system.*
- Leaching is mainly as a result of direct contact with the formulation under normal conditions of use.
- Leachables are typically a subset of extractables, and have potential to affect the product in various ways.

Extractables and Leachables

- **Extractables may be different than Leachables due to:**
 - **Different extracting conditions**
 - **Different time frames**
 - **A particular Extractable or Leachable can occur in more than one component of the container-closure system
e.g. Calcium from both plastic resin and elastomer**

Container-Closure System

- The sum of the packaging components that together contain and protect the dosage form. This includes both primary and secondary packaging components.
- **What Drug Packaging Should Do**
 - Storage : adequately preserve the integrity of the product
 - Deliver the drug e.g. prefilled syringes, Inhalers, ophthalmic
 - Protect the Drug product during shelf life
 - Packaging materials have been in the focus of such investigations for a long time as the contact time between drug product and packaging material is rather long.

Container-Closure System

- What Drug Packaging Should NEVER Do

 - Contribute harmful components to the drug
 - Increase Toxicity of the product
 - Carcinogenic / Genotoxic
 - Impact Drug Efficacy / Stability (e.g. cause precipitation or pH change)
- In most cases, harmful components originate from the package manufacturing process
- Manufacture of the Drug product
 - But in addition one should consider other possible sources of contamination - devices and equipment used in the production process itself, e.g. filters, gaskets, bags, tubes, containers.

Sources of extractables and leachables

- Plastic components - Vinyl Monomer & Plasticizers e.g. Phthalates. These are added to plastics to make them more flexible and can be found throughout the manufacturing process and in packaging materials - carcinogenic.
- Rubber: Nitrosamines, Vulcanizing Agents, Accelerators, polynuclear aromatic hydrocarbons (PAHs) - carcinogenic
- Many drug products are distributed / administered in packages made of plastic and rubber components : phthalates, PAHs, or nitrosamines could potentially come into contact with the drug product and be harmful.
- inks & adhesives from labels, coatings, antioxidants, catalyst residues, organic oligomers, heavy metals
- Metered-dose inhalers (MDIs), dry-powder inhalers (DPIs), and nebulizers can be complex because they may be constructed from a myriad of plastic, rubber, and stainless steel components.

- Fortunately, information on potential leachables may be obtained from the known ingredients of the rubber and plastic materials.
-

- For example :

- thiurams, dithiocarbamates, and mercaptobenzothiazoles are commonly used sulfur-containing curing agents in rubber manufacturing, hence, they are potential leachables in the drug product where sulfur-cured rubber is used.
- Polybutylene terephthalate (PBT) is a widely used polyester plastic in medical device and MDI valve components.
 - PBT oligomers and other residuals or degradants can be similarly leached from the valve components fabricated from this material.

Need & Importance for control

Control of extractables and leachables in drug products is important for ensuring :

Safety & Efficacy of drug products

- Can have considerable influence, especially highly active biopharmaceutical drug formulations, which may contain extremely small amounts of the active ingredient.
- Perhaps more important than the toxicology of such materials is their potential to elicit serious immunologic responses, even at extremely small dosages.

Quality & Stability of drug products

- Extractables and leachables pose problems at every stage
 - they may interfere with drug assays / medical diagnostic tests;
 - they may increase the impurity level of a drug product to an unacceptable level;
 - they may react with one or more drug product components

Extractables & Leachables : Testing in Packaging Materials

- Extractables and leachables are a growing concern for pharmaceutical manufacturers and regulatory bodies.
 - The development of unique packaging, novel formulations, delivery systems and drug-coated medical devices has exacerbated this issue
 - The increasing popularity of single-use disposables such as filters, tubing, and bags for biopharmaceuticals can introduce unwanted extractables into the final product.
 - US FDA demands more and more information about every packaging component and its potential to interact with the drug product.
- Drug manufacturers now invest a tremendous amount of time and money to identify, quantify, and minimize impurities related to their drug products so that the US FDA can make informed decisions regarding drug product purity and safety.

Leachables and Extractables – Regulatory Landscape

- Federal Food Drug and Cosmetics Act
- ~~Good Manufacturing Practices – 21 CFR~~
 - CFR 211.94 – Drug Product Containers and Closures
 - CFR 211.160 – General Requirements
 - D&C Act / Rules : Schedule M
 - EU Directives
- CDER Guidance Documents for Industry
- International Guidelines
 - EMEA
 - Health Canada
- Standard Compendia
 - USP / EP / IP / ICH Q4 (Annexures), Q6 A, Q8

Drug Regulatory Landscape

- An area of increasing concern and scrutiny for US FDA's Center for Drug Evaluation and Research (CDER) is the potential adulteration of drug products by extractable and leachable compounds that enter a drug from a container, closure system, disposable, or device.
- Addressing this concern, 21 *CFR* 211.94 a) states that:
 - Drug product containers and closures **shall not be** reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements
 - Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product

Drug Regulatory Landscape

US Food, Drug and Cosmetic Act *Section 501(a)(3)* :

- A drug is deemed to be adulterated if its container is composed in whole or part of any poisonous or deleterious substance which may render the contents injurious to health

Biologics *21CFR600.11(h)* :

- All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use.
- All final containers and closures shall be clean and free of surface solids, **leachable** contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use.

Drug Regulatory Landscape

- In May of 2005, the European Agency for the Evaluation of Medical Products (EMA) issued the *Guideline on Plastic Immediate Packaging Materials*, which indicates that
 - “the aim of extraction studies is to determine those additives such as antioxidants, plasticizers, catalysts, initiators, etc.) that might be extracted by the active substance in contact with the plastic material. Extraction studies are considered necessary for plastic materials used for container systems of nonsolid active substances and nonsolid dosage forms.”
- EMA specifies that:
 - interaction studies between the plastic packaging material and the active substance should be evaluated.
 - In addition, migration studies are deemed "necessary when extraction studies have resulted in one or several extractables"

Schedule M

■ 17.2 For product containers and closures. -

- all containers and closures intended for use shall comply with the pharmacopoeial requirements.
- Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug.
- *Glass Bottles.*- made of USP Type-I and USP Type-II glass shall only be used. USP Type-II bottles shall be validated for the absence of particulate matter generated over a period of the shelf life of the product and shall be regularly monitored after the production, following statistical sampling methods.

Schedule M : Specific Requirements For Product Containers and Closures for **sterile products**.

- All containers and closures intended for use shall comply with the pharmacopoeial and other specified requirements.
- Suitable samples sizes, specifications, test methods, cleaning procedures and sterilization procedures, shall be used to assure that containers, closures and other component parts of drug packages are suitable and are not reactive, additive, adsorptive or leachable or presents **the risk of toxicity** to an extent that significantly affects the quality or purity of the drug.
- Plastic granules shall also comply with the pharmacopoeial requirements including physio-chemical and biological tests.
- It shall be ensured that containers and closures chosen for a particular product are such that when coming into contact they are not absorbed into the product and they do not affect the product adversely. The closures and stoppers should be of such quality substances as not to affect the quality of the product and avoid the risk of toxicity.
- *Rubber Stoppers*. - The tuber stoppers used for Large Volume Parenterals shall comply with specifications prescribed in the current edition of the Indian Pharmacopoeia.

FDA Industry Guidances

- Numerous guidances mention the appropriate evaluation of packaging components.
-
- EMEA - Committee for Proprietary Medicinal Products (CPMP):
 - *Note for Guidance on Development Pharmaceuticals*
 - *Development Pharmaceuticals for Biotechnological and Biological Products, Annex : Guidance on Development Pharmaceuticals*
 - ICH :
 - *Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances*
 - *The Common Technical Document for the Registration of Pharmaceuticals for Human Use, Quality*
- These guidances recommend that the safety and compatibility of the dosage form with the primary container closure system be established early in the development process.
 - Specific focus is on the potential for drug-biologic interaction with the container or closure because of leaching or absorption.

FDA Industry Guidances

- FDA Guidance for Industry – *Container Closure Systems for Packaging Human Drugs and Biologics* (1999)
 - Addresses the review and evaluation of packaging requirements.
 - According to this document, each New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) should contain enough information to demonstrate that a proposed container closure system and its components are suitable for its intended use.
 - The type and extent of information required will depend on the dosage form and route of administration.
 - CDER and CBER guidance document details QC expected of a container closure system to be used in the packaging of drugs and biologics - understanding the levels of extractables and leachables, the test methods related to these contaminants, and other considerations relating to packaging components - Outlines a risk based approach.

FDA Guidance for Industry – *Container Closure Systems for Packaging Human Drugs and Biologics* (1999)

- Qualification and quality review is applied to packaging materials .

- Packaging suitability is based on four attributes: protection, safety, compatibility and performance (function and/or drug delivery).

- For injectable dosage forms, outlines the tests required to show that interaction is not a problem. Associated components, such as those used only at the time a dosage is administered, self-adhesive labels and secondary packaging materials, are also included in the review process.

- Also specifies that: "*... packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with a drug product. These applications should contain an extraction study on the packaging component to determine which chemicals and/or residues may migrate into the dosage form, and a toxicological evaluation of the substances...*"

- **FDA's May 1999 container-closure guidance has accelerated the requirements for extractable and leachable testing of container-closure packaging components.**

FDA Industry Guidances

- Inhalation and injection drug products have the highest requirements.
-
- There are product-specific draft guidelines for metered dose inhalers (MDI), dry powder inhalers (DPI), nasal sprays and inhalation solutions, suspensions and spray drug products.
 - Inhalation and injectable drug products have stringent requirements - identity and concentration of leachables in inhalation and nasal drug products must be monitored throughout the products' shelf life
 - **FDA Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1998)** – details testing & documentation requirements of MDIs and DPis in NDA's and ANDA's
 - **Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (2002)** – details Toxicological evaluation of extractables from each of the components & appropriate *in vivo* / *in vitro* tests to be submitted

FDA Risk analysis

Degree of concern Associated With Route of Administration	Packaging Component-Dosage Form Interaction High	Packaging Component-Dosage Form Interaction Medium	Packaging Component-Dosage Form Interaction Low
Highest	Inhalation Aerosols & Solutions•Injections &Injectable Suspensions	Sterile Powders & Powders for Injection	
High	Ophthalmic Solution, Suspensions•Transdermal Ointments & Patches• Nasal Aerosols & sprays		
Low	Topical Solutions & Suspensions•Topical & Lingual Aerosols•Oral Solutions & Suspensions	Topical & Oral Powders	Oral Tablets Oral Capsules

FDA Trigger

- FDA's interest in this area is believed to be in response to a particular incident in the late-1990s in which an MDI was found to contain harmful leachables.

- Leachables in inhaled drug products tend to arise from polymers, elastomers, adhesives and curing agents, metal components, dyes and pigments, and mold release agents
- In another case, the supplier of the rubber O-ring in a device wasn't accustomed to the standards of the pharmaceutical industry and formulated the rubber using some polynuclear aromatics (PNAs), creating a health risk. Since then, the agency has asked for more analysis with submissions.
- Some other cases : reports of PNAs in elastomers, PNAs in MDIs, volatile N-nitrosamines present in baby bottle rubber nipples, and mercaptobenzothiazole (2 MBT) in elastomers

- Glass Vial Case Study:
 - Problem: Particulates (up to 150 μm) were observed in product containing a phosphate buffer after switching from a molded glass vial to a tubular glass vial
 - Source: Particles identified as aluminum phosphate from aluminum in the glass tubing vials

 - Resolution: Inside of vials coated with baked-on silicone
-
- Wyeth (2006) :
 - investigation into various unknown peaks occurring in drug products had identified phenol as a packaging extractable originating from ink used to print package inserts.
 - However your firm later identified the unknown peak as Caprolactarn, an extractable that potentially originated from Nylon components used to pack the drug”
-
- Non-container case study
 - Problem: Phenolic compounds found in a peptide product during release testing•
 - Source: Phenolic compounds were absorbed from a cleaning agent for rubber gaskets used in the filling lines•
 - Resolution: Rubber gaskets were replaced by Teflon lined rubber gaskets that did not absorb phenolic compounds

Regulations : Potential Issues

- FDA provides guidance for protection against extractables and leachables in various documents : therefore, the qualification and quality control of all components coming into contact with the drug formulation is an integral part of any FDA application process.
- Extractables and leachables issues often are not addressed up front and ultimately can cause regulatory delays for the drug manufacturer.
- The development, validation, and testing of these components must be carried out under ICH and USP guidelines in a cGMP compliant laboratory
- The activities : time consuming, require expertise and a wide array of analytical techniques. Drug manufacturers may not have the resources available & outsource these activities to contract laboratories.
- It is also imperative that the component vendors, laboratories, toxicologists, and the regulatory agency have open, effective, and timely communication – work collaboratively.

Collaboration

- The Product Quality Research Institute (PQRI) was established to conduct research that generates scientific information to support the development of regulatory policy.
- PQRI is a nonprofit foundation that serves as a vehicle for FDA (CDER), industry (e.g. PMRA, PDA) and academia to collaborate on key issues in pharmaceutical product quality through research and expert analysis.
- The PQRI Extractables and Leachables Working Group has developed and submitted to FDA a document entitled “Safety Thresholds and Best Practices for Leachables and Extractables Testing in Orally Inhaled and Nasal Drug Products.” - Threshold approach to qualify leachables

Current Drug Laws, Regulations, Guidances : How do they address identified four key areas

- Analytical Characterization of Extractables (Control Extraction Studies) - the specific requirements for control extraction studies
- Analytical Characterization of Leachables - How is a correlation with extractables established?
- Safety Qualification of Leachables -What are current industry practices for establishing safety of leachables (e.g., What are the qualification criteria?)
- Routine Extractables Testing - Is quantitative testing of extractables appropriate for control of composition of all components? (a control strategy combining appropriate scientific practices, cGMP controls and supplier qualification systems for ensuring the relevant performance and safety characteristics of critical components)

FDA's Quality Control Approach

- Characterize/Identify all possible extractables and establish a profile for each packaging component
- Establish a correlation between extractable and its leachables potential
- Set meaningful acceptance criterion for a given extractable in corresponding incoming packaging components, based on its qualification level and actual observed data
- Set meaningful acceptance criterion for a given leachable based on actual observed data in the drug product

Evaluation of Extractable and Leachables : Guidelines

■ Factors to be Considered :

- materials of construction of the systems, surface treatments and/or processing aids, dosage form active ingredients and excipients, sterilization and/or other related processing, and storage conditions.
 - Review composition of primary packaging components with vendors, obtain certificates of compendial compliance
 - Identify potential Extractables & Leachables with assistance from vendors, literature search – MSDS, Technical Data Sheets
 - Use of clean raw materials with minimal processing additives, extractables and leachables are minimized.
- **Characterizing the materials and the chemicals** that can migrate or extract from container-closure system components to the drug product - critical to understanding the biological safety and suitability of a container.

■ **Extractables :**

- Perform extraction studies with solvents representative of the drug product,
- Testing under stressed conditions (solvent, temp, time) should demonstrate:

 - that the extractable profile is acceptable for the specific dosage form and
 - that levels observed will not be approached or exceeded during the shelf life of the drug product.

■ **Leachables :**

- Develop test methods for selected potential Leachables for stability studies
 - Identify, quantify and assess safety of leachables, Develop limits for Leachables
 - Leachables are substances identified in a defined laboratory regimen by simulating use conditions.
- A container-closure system found acceptable for one drug product cannot be assumed to be appropriate for another.

Thank You.....