

Extractables & Leachables

Regulatory perspective

Gautama Buddha

Extractables

- **Extractables—compounds extracted from the container-closure system into the drug or biological product by exertion of an artificial force (“Exaggerated Conditions”)**
- **e.g.**
- **Stronger solvent**
- **Higher temperature**
- **Longer time**



Leachables

- **Leachables—compounds that migrate from the container-closure system into the drug or biological product under normal conditions of use or during stability studies (“Normal Conditions”)**
- **Leachables are a subset of Extractables**



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**



Historical concerns

- **Rubber: Accelerators, Nitrosamines, Vulcanizing Agents**
- **Plastics: Vinyl Monomer, Plasticizers**
- **Labels: Inks & Adhesives**
- **Pallets: Tribromophenol**



Other sources of Leachables

- **Manufacturing Equipment**
 - Filters
 - Gaskets
 - Tanks
 - Tubing
- **Secondary Packaging**



Importance

- **May increase toxicity of drug product**
- **May interfere with drug product assay**
- **May react with one or more of the drug product components (e.g. may cause precipitation or pH change)**

Container Closure System

- Refers to the sum of the packaging components that together contain and protect the dosage form. This includes both primary and secondary packaging components.
- Packaging system= Container closure system



FDA Regulations and Guidelines

- **21 CFR §211 cGMP For Finished Pharmaceuticals**
- **§211.94 Drug Product Containers & Closures**
- **(a) 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**

Current Regulatory Landscape

- **FDA Guidance documents**
- **ICH Guidance**
- **EMA Guidance**
 - Threshold for Toxicological concern**
- **IPAC-RS**
 - Response to FDA draft guidance**
- **PQRI**
 - Threshold approach to qualify leachables in OINDP**

FDA Risk analysis table 1

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 Attachment C

- **Extraction Studies on Packaging Components**
- **USP characterization tests <381> for elastomers & <661> for plastics**
- **USP biological reactivity tests <87> & <88> on plastics or elastomers**
- **Obtain qualitative & quantitative extraction profiles of plastics or elastomers**



FDA Attachment C

- **Evaluate whether FDA indirect food additive regulations provide an adequate indicator of safety**
- **Ideal solvent used for extraction study will be one having the same propensity to extract substances as the dosage form**
- **Use a stronger extracting solvent than drug product to obtain a qualitative extraction profile**



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**



Determination of Extractables & Leachables from Container-Closure Systems

- **Gather information on Possible Extractables:**
- **MSDS**
- **Technical Data Sheets**
- **Confidential Information on Qualitative Composition**
- **Extractable Profile in Water from Vendor**
- **Categorize Materials**
Glass, Plastic, Elastomeric etc.

Determination of Extractables & Leachables from Container-Closure Systems

- **Review composition of primary packaging components with vendors and obtain certificates of compendial compliance**
- **Identify potential Extractables & Leachables with assistance from vendors, literature search, primary screening**
- **Perform extraction studies with solvents representative of the drug product**
- **Identify and quantify Extractables**

Determination of Extractables & Leachables from Container-Closure Systems

- **Compare Extractables with list obtained from component supplier or plastic resin vendor**
- **Assess safety (concentration, route of administration, dose regimen etc.)**
- **Develop test methods for selected potential Leachables for stability studies**
- **Identify, quantify and assess safety of leachables**
- **Develop limits for Leachables**

Non-Volatile Residues

- **USP <661> Containers –Plastics**
- **120 cm²/20 mL purified water**
- **Extract at 70 deg C for 24 hours**
- **Evaporate to dryness**
- **Further evaporate at 105 deg C for 1 hour**
- **Mass difference between sample and blank is Non-Volatile Residue**
- **Sample also used to test for Heavy Metals,**
- **Buffering Capacity & Residue on Ignition**

Extraction Vehicles for Biological Tests

- **Sodium Chloride injection**
- **Polyethylene Glycol 400**
- **Vegetable oil (Sesame oil or Cottonseed oil)**
- **Drug product vehicle**
- **Water for Injection**

Extraction Conditions for Biological Tests

- **USP <88>, ISO 10993-11**
- **Surface area varies according to form of material**
- **Tubing with 0.5 mm or greater wall uses 3 Sq cm/mL**
- **Molded items (stoppers) 3 Sq cm/mL**
- **Temperature**
- **37 ±2 deg C for 72 hours ±2 hours (ISO only)**
- **50 ±2 deg C for 72 hours ±2 hours**
- **70 ±2 deg C for 24 hours ±2 hours**
- **121 ±2 deg C for 1 hour ±0.2 hour**



Determination of Extractables & Leachables from Container-Closure Systems

- **No single procedure for managing Extractables and Leachables**
- **The procedure is dependent upon many factors including:**
 - **Route of administration**
 - **Duration of administration**
 - **Patient population**

Elastomer Case Study

- **FDA Case Study:**
- **Problem:** Butylated hydroxy toluene(BHT) was observed in a lyophilized product at 12 months after switching from latex to a chlorobutyl stopper
- **Source:** BHT, a common food additive, was found at very low levels and has very low toxicity. Its source was the butyl rubber stopper
- **Resolution:** Set acceptance level for BHT and continue to monitor BHT levels

Ingrid Markovic, FDA CDER American Pharmaceutical Review Pages 96 –101, May-June 2009

ElastomerCase Study

- **Problem:** Particles (10 to 200 μm) observed in diluent vials containing a phosphate buffer at 6 months
- **Source:** Particles identified as zinc phosphate. Zinc oxide is present in the bromobutyl stopper. Leached [zinc ion] required to form precipitate was only 224 ppb
- **Resolution:** Switch to a chlorobutyl stopper that does not contain zinc

CastnerJ. et al. American Pharmaceutical Review Pages 70 –75, March –April 2004

Glass Vial Case Study

- **FDA 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

*Ingrid Markovic, FDA CDER American Pharmaceutical Review Pages 96 –101,
May-June 2009*

Tungsten Case Study

Problem:

- **Visible protein particles (10 to 100 μm) were observed in new lots of pre-filled glass syringes with a staked needle filled with an alpha helical protein at pH 4.0 at Amgen**
- **Particles contained tungsten**
- **Source: Tungsten pins are used to maintain the fluid channel during forming of the syringe cone at $> 1,000^\circ$**

CLiu et al. J. Pharm. Sci. Technol.64, 11-19, 2010

Eporex[®] Case Study: Background

- **Eporex[®]-a brand of recombinant erythropoietin (epoetinalpha) marketed outside of the U.S. In pre-filled syringes used to treat anemia**
- **European regulatory authorities requested removal of Human Serum Albumin from formulation**
- **New formulation launched 1998 with polysorbate80 replacing HSA as stabilizer**

Eporex[®] Case Study

- **Problem:** Increased incidence of anti-body mediated Pure Red Cell Aplasia (PRCA) –severe and rare form of anemia following introduction of reformulation in pre-filled syringes
- **Source:** Polysorbate 80 caused the presence of a number leachables in formulation from the rubber plunger. Compounds were aromatic phenols and mercaptophenols related to vulcanizing agent for butyl rubber
- **Resolution:** Uncoated plunger replaced by a coated plunger –adverse events return to pre-polysorbate 80 levels
- Pang et al. J. Pharm. Sci. Technol.61, 423 –432, 2007



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

Ingrid Markovic, FDA CDER American Pharmaceutical Review Pages 20 – 27, Sept-Oct 2006



Non container case study

- **Problem:** Complaints of uncharacteristic moldy, musty or mildew-like odor beginning in 2008
- **Investigation:** Determined that cause was not microbiological in 2008. Found that once tablets were removed from bottles, they did not have the uncharacteristic odor but containers retained a strong odor
- **Source:** Hypothesis is that wooden storage pallets were treated with 2,4,6 tribromophenol(TBP) as a pesticide and flame retardant .

TBP degrades to 2,4,6 tribromoanisole(TBA) which is organoleptically detectable at parts per trillion



Summary on Extractable & Leachables

- **Rationale –The reasons for the need to study Extractables& Leachables are clear**
- **Regulatory Requirements –The legal requirements to study Extractables& Leachablesare clearly stated in FDA, CPMP and ICH Guidelines**
- **Study Design –Regulatory Guidelines lack details**



Proactive steps

- **Help from Testing laboratories**
- **Involve vendor in development process**
- **Understand mfg. process Packaging system**
- **Explore options**

Coated Vs uncoated stoppers

Low migration adhesives



Thanks