

# Leachable and Extractable Testing

## A Primer on Regulations and Methods

As presented to



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WHEN YOU NEED TO BE SURE



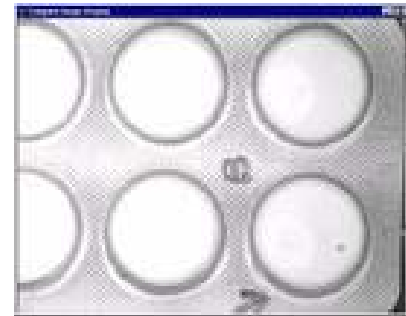
“I need a Leachable and Extractable Test”



?

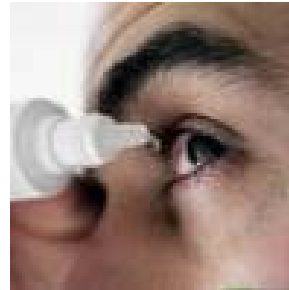
## What does Drug Packaging Do?

Stores the drug



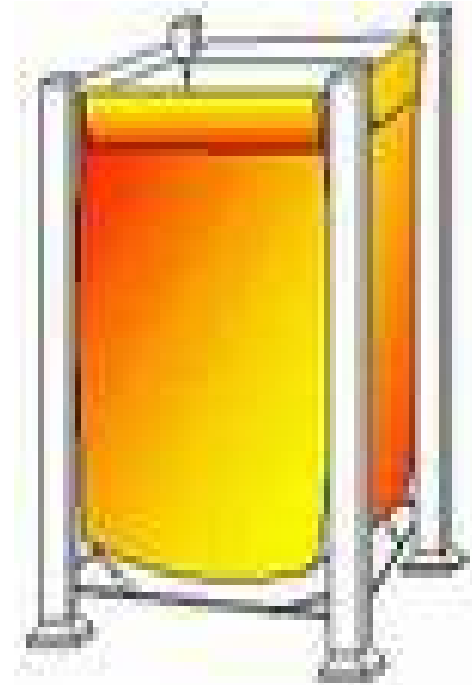
## What does Drug Packaging Do?

Delivers the Drug



## What does Drug Packaging Do

Manufactures the drug



## What does Drug Packaging do?

Protects the Drug



## What Drug Packaging Should NEVER Do

Contribute harmful components to the drug

- Toxic
- Genotoxic or Carcinogenic
- Impact Drug Efficacy

Harmful components that can originate from the package manufacturing process:

- Plasticizers
- Heavy metals
- Phthallates, polyaromatic hydrocarbons, nitrosamines, etc.

## Review of the Regulations (LAWS)

- 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
  
- Good Manufacturing Practices *21CFR211.94(a)*
  - Drug product container and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality or purity 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

- **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.

## Review of the Regulations (GUIDANCES)

- FDA Guidance for Industry – Container Closure System for Packaging Human Drugs and Biologics (1999)
  - CDER and CBER guidance document details QC expected of a container closure system to be used in the packaging of drugs and biologics
  - Outlines a risk based approach
- FDA Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1998)
  - CDER guidance document detailing testing and documentation required of MDI's and DPI's in NDA's and ANDA's.

## Review of Regulations (GUIDANCES)

- Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (2002)
  - Toxicological evaluation of extractables from each of the components should be submitted.
  - Appropriate *in vivo* and *in vitro* tests should be submitted

## Review of Regulations (FDA actions)

### Evans Vaccine (2003)

The inspection noted the lack of filter extractable validation studies on filtered []monovalent and trivalent bulks

### Similasan AG (August 2005)

“Further it is unclear to us whether you have conducted filter extractable and leachable testing with product. If you have this data, provide it to us. If you do not, let us know when you will be able to provide it to us.”

### Wyeth (2006)

“Your previous investigation into various unknown peaks occurring in your 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”

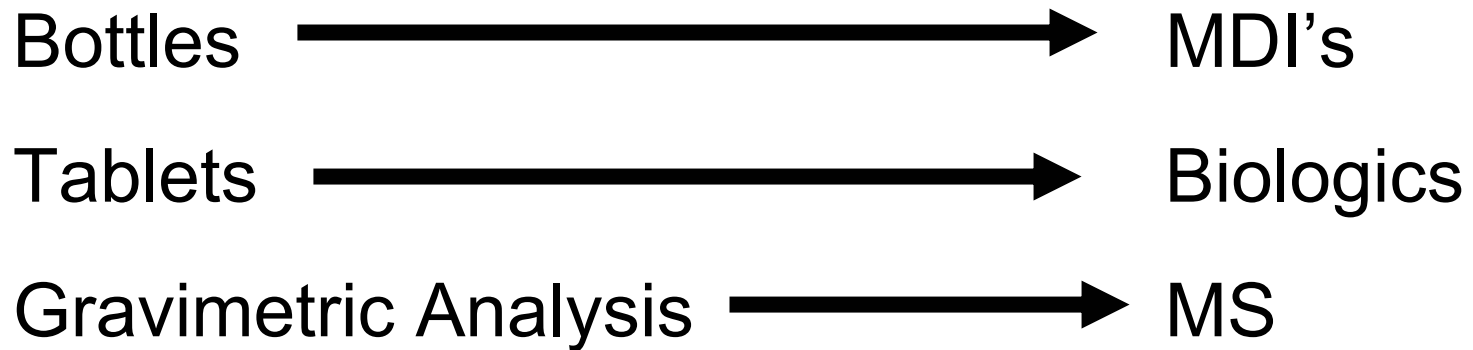
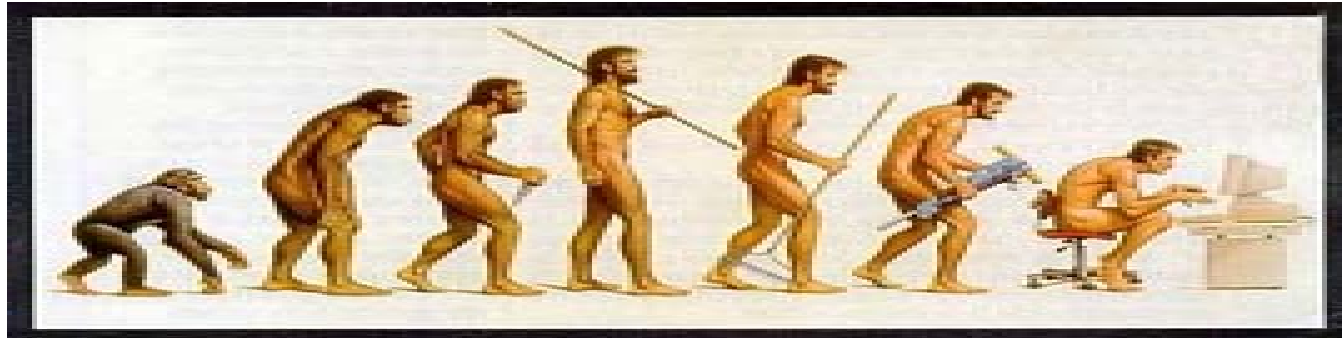
## Which tests??



- Begin with the end in mind
  - What product?
  - What patient population?
  - What package

Beginning at the end will  
give you a good  
indication where to start.

## Complexity of Tests and Tools Evolve



Risk Associated with the Route of Administration	Likelihood of Package- Drug Interaction		
	High	Medium	Low
Highest	Inhalation aerosols and solutions Injections	Sterile powders and powders for injection Inhalation powders	
High	Ophthalmic solutions Transdermal ointments and patches Nasal sprays		
Low	Topical Solutions Topical and Lingal aerosols Oral solutions	Topical Powders Oral Powders	Oral Tablets and Capsules

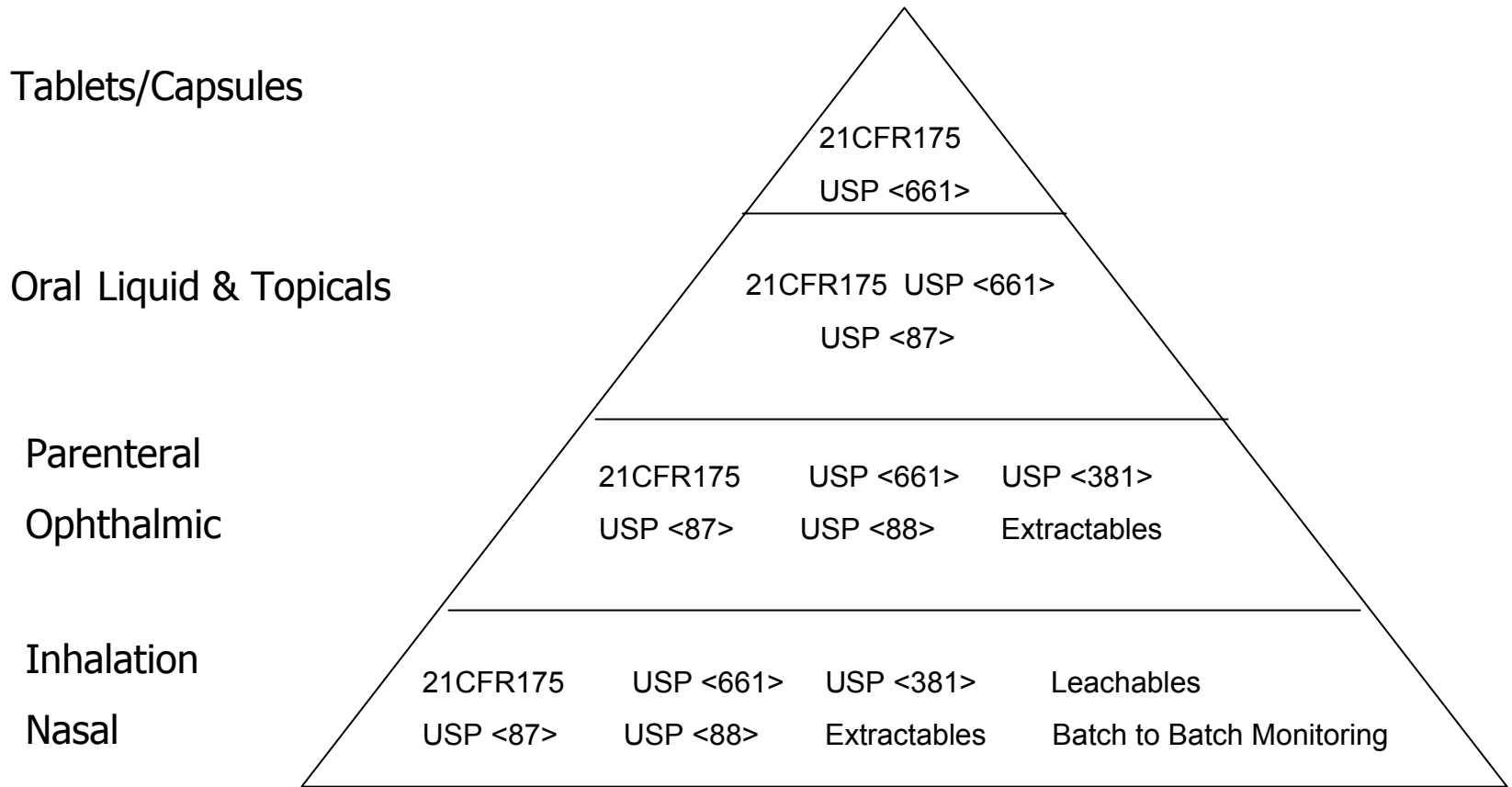


## Tests that Confirm Packaging Protection Capabilities

- USP <661> Light Transmission
- USP <661> Water Vapor Permeation
- USP <671> Container Closure Testing
- Dye Ingression Studies
- Microbial Ingression Studies

4S	Indirect Food Additives USP Physicochemical	Tablets, Capsules Topical Powders
3S	All of 4S + In vitro bioassay	Topical solutions Oral Powders
2S	All of 3S + Biological Reactivity Possibly extraction evaluation	Injectables Ophthalmics
1S	All of 4S + Extraction evaluation Batch to batch monitoring	Inhalation Nasal Sprays

# Increasing Complexity



- Glass: Water Attack
  - Extraction
- Glass: Arsenic
  - 1 ppm



## USP <661> Physicochemical (PE and PP)

- Extraction
- Nonvolatile residue
- Residue on Ignition
- Heavy Metals
- Buffering Capacity

## USP <661> PET & PETG (liquid oral dosage)

- Extraction
  - Purified Water
  - 25% Alcohol
  - 50% Alcohol
  - N-Heptane
  - 49 C for 10 days
- Total Terephthaloyl Moieties
  - Spectrophotometer
  - Ppm level
- Ethylene Glycol
  - Spectrophotometer
  - Ppm level

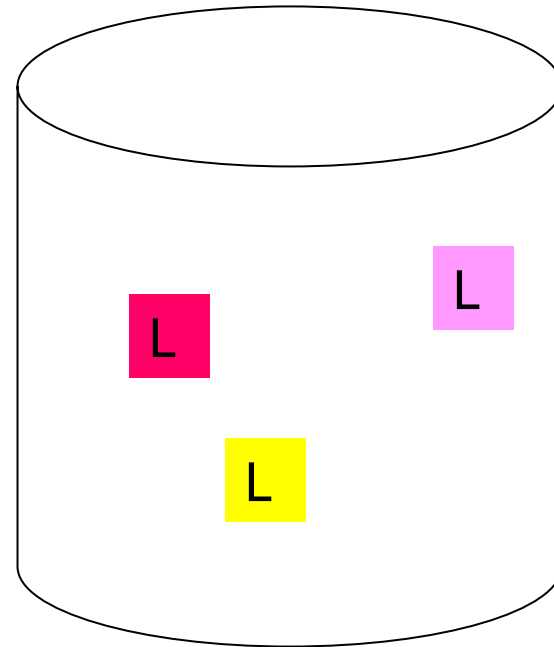
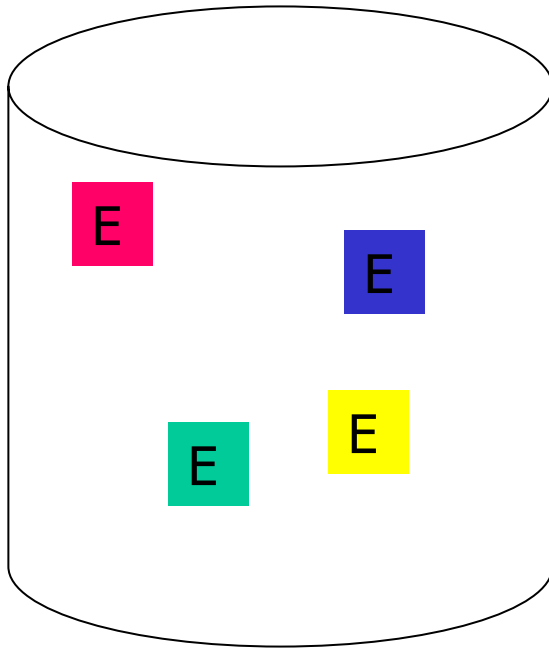


## USP <381> Elastomeric Closures

- Extraction
  - Purified Water (121C for 2 hours)
  - Isopropyl Alcohol (Reflux 30 minutes)
  - Drug Product (Reflux 30 minutes)
- Turbidity
- Heavy Metals
- Reducing Agents
- pH Change
- Total Extractables
  - Gravimetric
  - mg

## What is Leachable and Extractable Testing

- Extractable: **Any** chemical species that can be removed from a packaging component under abusive laboratory conditions
- Leachable: an extractable that actually migrates into a drug product under storage conditions



- Not all Extractables are Leachables
- Not all Leachables correlate to Extractables

- Extract
- Identify
- Assess the risk
- Develop the Method
- Validate the Method in Drug Product
- Perform Leachable Study (Stability)



- Use methods outlined in USP <661> or <381>
  - Cut samples into small pieces
  - Extract with solvents that make sense for the container component and the final product
  - Extreme temperature and time will give worse case scenario
  - Reference compendial methods

- Identify Extractables through analytical testing:
  - LC/MS
  - GC/MS
  - ICP/MS
- Detection limit is much enhanced with these technologies
  - Versus the gravimetric/colormetric analysis of USP methods
  - Ppb vs ppm
- Work with container manufacturer to identify extractables
  - Vendor may not always be willing to share information
  - Trade secrets, proprietary information
  - Advantage to working with 3<sup>rd</sup> party lab

## Assess the Risk

- Literature Search
- Toxicology Testing
  - USP <87>
  - USP <88>
- Is there a risk of product interference
- Is there a risk of assay interference.

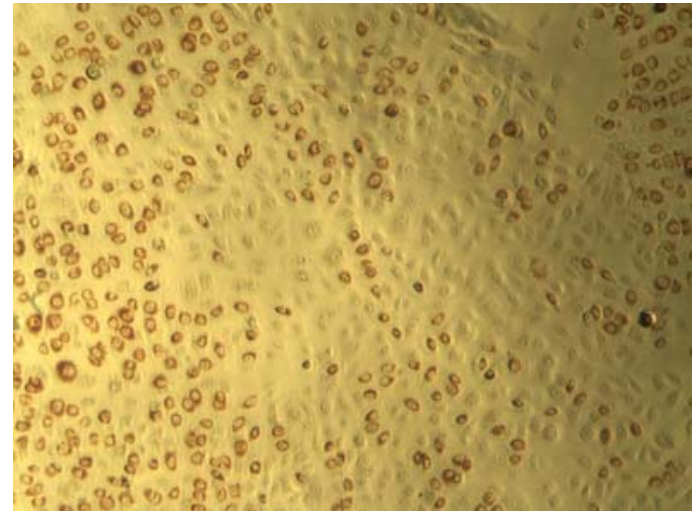
## ■ ICH Guidelines

- Accuracy
- Precision
- Specificity
- LOQ
- Linearity
- Range

## Leachable Study

- Stability lots
  - Accelerated
  - Room temperature
- Risk assessment again if found
  - Quantities
  - Drug Product Interaction
  - Assay interference

- At the end of the day, we are most concerned with the biological effect of these compounds
- Does an extract of the material have an impact on cells grown in tissue culture?
- Grow a monolayer of mouse cells
- Cut up package and extract in Growth medium for 24 hours.
- Replace growth medium from tissue culture and replace with extract growth medium.
- Examine cells after 48 hour contact time.



## Is USP <87> the best indicator of toxicity?

- USP <381> Elastomeric Closures states: “Materials that do not meet the requirements of the *in vitro* tests are subjected to the second stage of testing (USP <88>)
- USP <661> Plastics and Other Polymers states: “Materials do not meet the requirements .... are not suitable for drug products.”
- Not all tests that pass *in vitro* test will pass *in vivo* test.
- Not all products that fail *in vitro* tests will fail *in vivo* tests.

## ■ Systemic Injection

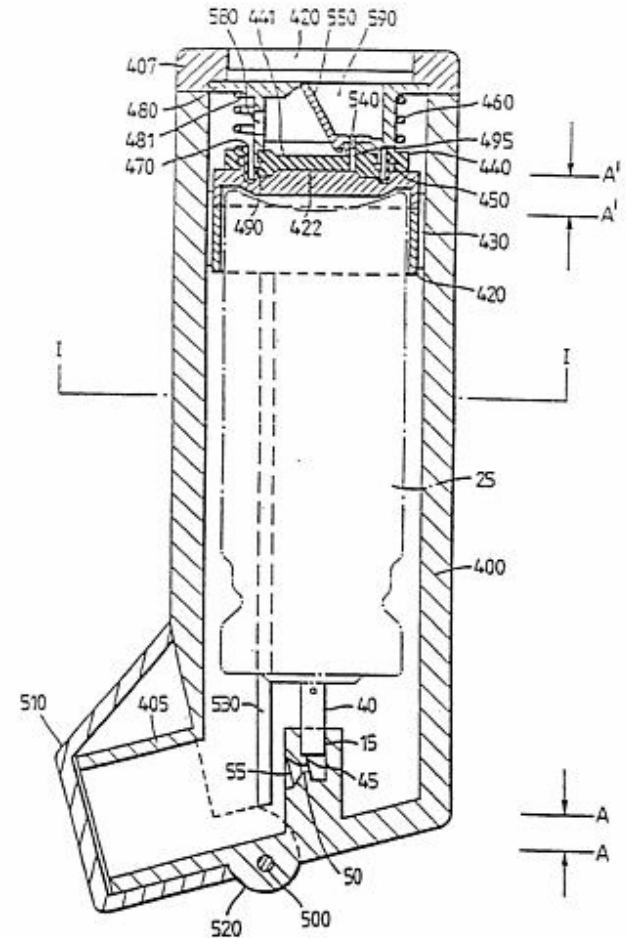
- Biological response to single dose infection
- Extracted in NaCl, 5% EtoH in NaCl, PEG 400, vegetable oil
- Intravenous or intraperitoneal injection.

## ■ Intracutaneous Injection

- Biological response to single dose
- Extract in NaCl, Alcohol, PEG400, and Vegetable Oil
- 24, 48, and 72 hour observation
- Erythema and edema

## Case Study

- USP <661> <381>
- USP <87> <88>
- GC/MS
- LC/MS
- ICP
- MD
- MV
- Stability



- FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, (1999)
  - [www.fda.gov/cder/guidance/1714/pdf](http://www.fda.gov/cder/guidance/1714/pdf)
- FDA Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (1999)
- Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (2002)
- USP <661> Containers
- USP <381> Elastomeric closures
- USP <87> Biological Reactivity Tests – In vitro
- USP <88> Biological Reactivity Tests – In vivo
- 21CFR175: Indirect Food Additives
- EP 5.05: 3.1 Materials Used for the Manufacture of Containers
- EP 5.05: 3.2 Containers



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