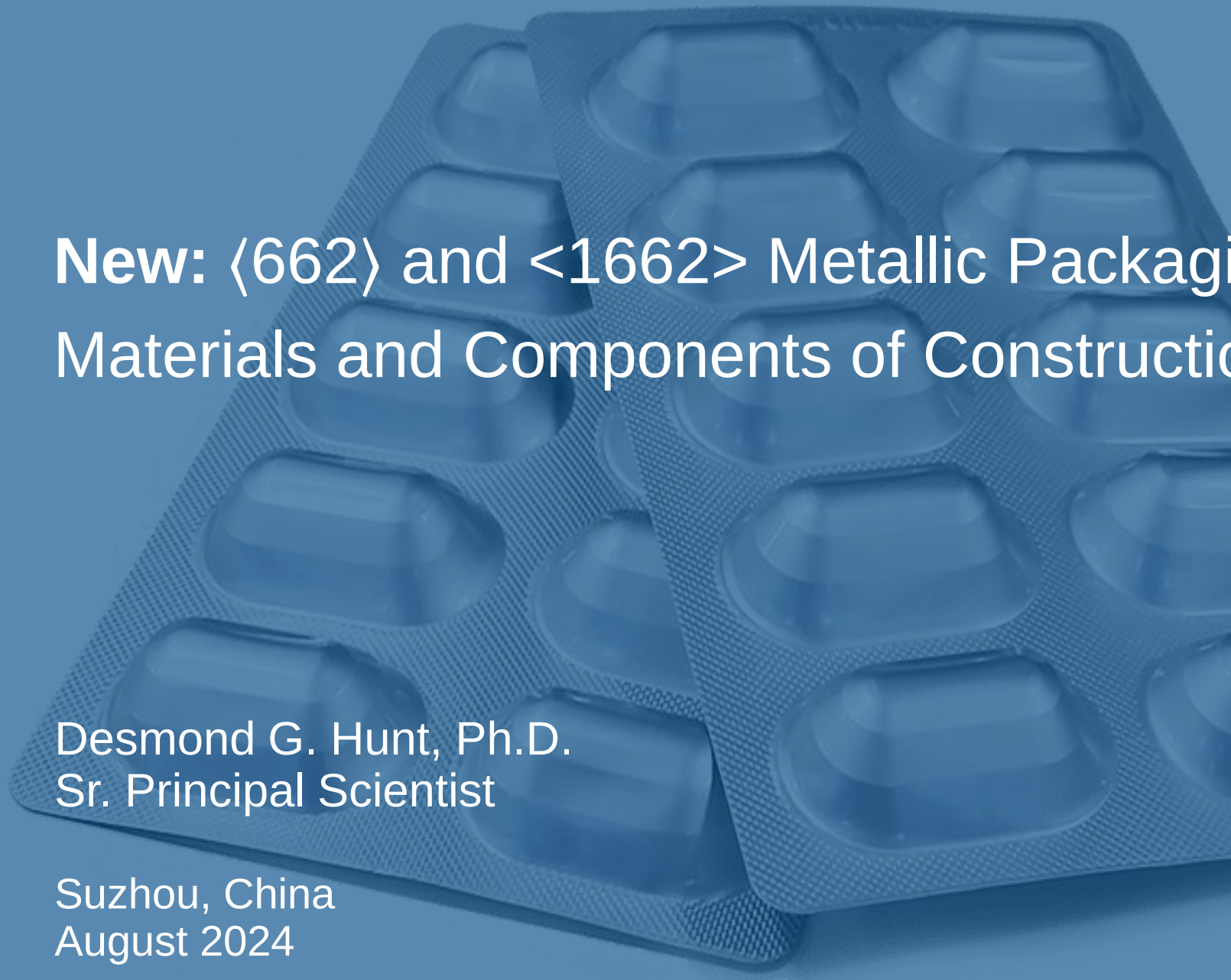
New: ⟨662⟩ and <1662> Metallic Packaging Systems and Their Materials and Components of Construction



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August 2024

Historical: Metal Packaging in Pharmaceuticals

Early Usage

- **Early 1900s**
  - **Stip Tube:** Introduced as the first ophthalmic or eye-tip tube
  - **Syrette:** An early device with two collapsible tubes for injecting liquids. It evolved into a metal tube with a hypodermic needle, widely used during WWII (over 70 million manufactured)
- **1940s - 1950s**
  - **Metal Tubes:** Used for various ointments. Metal tube's impermeability to light and air preserved product potency and prevented contamination
- **1960s**
  - **Foil Strip Packs:** Introduced, followed by aerosols, squeeze packs, and blisters. Blisters were designed to improve patient compliance
- **1980s Growth**
  - **Blister Packs:** Rapid growth, driven by advocacy for original packed dispensing (OPD). OPD reduced tampering, contamination, and dispensing errors

Modern Usage

- Metal packaging systems are now widely used for:
  - Primary and secondary packaging
  - Auxiliary packaging components

Key Benefits

- **Barrier Properties:** Blocks light, oxygen, moisture, and gases
- **Durability:** Withstands mechanical stress
- **Tamper Evidence:** Features to detect tampering
- **Sustainability:** Easy to recycle and environmentally friendly
- **Customization:** Various shapes, sizes, and finishes for branding.

USP Standards Gap: Metal Packaging

USP Packaging Material Standards

- **Elastomeric Materials:** <381> - *Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems*
- **Glass Packaging:** <660> - *Containers Glass*
- **Plastic Packaging**
  - <661> - *Plastic Packaging Systems and Their Materials of Construction*
  - <661.1> - *Plastic Materials of Construction*
  - <661.2> - *Plastic Packaging Systems for Pharmaceutical Use*

USP Metal Packaging Standards

- **Gaps in Existing Standards:** Unlike elastomer, glass and plastic, USP currently lacks guidance for metal packaging systems.

New USP Chapters for Metal Packaging

New Chapters

- <662> Metallic Packaging Systems and Their Materials and Components of Construction
- <1662> Materials and Manufacturing Processes for Metallic Packaging Systems

Objectives

- To create a minimal standard for metal packaging systems

Collaboration with Chinese Pharmacopeia (ChP)

- **Global Alignment:** Align standards for cross-border compliance
- **Key Activities:** Joint research, regular meetings, and shared scientific information

<662>: Metallic Packaging Systems and Their Materials and Components of Construction

USP Chapter <662>: Characterization of Metal Packaging Systems

Focus

- Functional & chemical analysis of metal packaging system

Scope

- **Primary Packaging Systems**
  - **Aerosol Cans**: For topical and inhaled products
  - **Blister Packs**: For solid oral dosage forms
  - **Soft Aluminum Tubes**: For topical dosage forms
  - **Canisters**: For inhaled drug products
  - **Aluminum Foil Backing**: For transdermal devices
  - **Foil Pouches & Overwraps**: For secondary packaging
- **Pharmaceutical Dosage Forms**
  - Aerosols, Capsules, Creams, Emulsions, Foams, Lotions, Ointments, Pastes, Suppositories, Tablets

Key Tests

- **Functional**
  - Burst Pressure, Particulate Matter, Surface Coatings, Tube Air Tightness, Tube Deformation, Foil Pinholes
- **Chemical**
  - Extraction

Functionality Tests

Burst Pressure Test

- **Purpose**: Ensures metal containers withstand internal pressures without deforming or leaking
- **Procedure**
  - **Mounting**: Place canister in a holding fixture
  - **Filling**: Fill with hydraulic oil
  - **Pressure Increase**: Raise pressure up to 300 psi
- **Acceptance Criteria**
  - **Deformation**: No visible deformation at 230 psi
  - **Leakage**: No leakage at 300 psi
- **Importance**: Validates structural integrity under extreme conditions

Particulate Matter Test

- **Purpose**: Evaluates for particulate contamination inside metal containers
- **Methods**
  - **Light Obscuration Particle Count** (Preferred): Detects particles ≥10 µm and ≥25 µm
  - **Microscopic Particle Count**: Alternative method
- **Acceptance Criteria**: Varies based on container volume
  - Based on USP <788> and <789>
    - Example: No more than 6000 particles per container for smaller volumes
- **Importance**: Ensures packaging does not introduce unacceptable particulate contamination into drug products

Functionality Tests: Surface Coatings

Canisters and Cans

1. **Coating Continuity (Porosity) Test – Copper Sulfate Test**
   - Checks anodic oxidation coatings on aluminum surfaces (thickness <5 µm) using copper sulfate.
2. **Coating Continuity (Porosity) Test – Sodium Chloride Test**
   - Assesses anodic oxidation coatings using sodium chloride to measure conductivity.
3. **Amplitude-Sensitive Eddy-Current Test**
   - Measures coating thickness using eddy currents generated by a probe.
4. **Coating Surface Free Energy Test – Contact Angle Test**
   - Measures surface free energy using contact angle to assess potential drug interaction.
5. **Coating Adhesion – Compression Test**
   - Assesses adhesion of internal lacquer coatings.
6. **Coating Thickness Test**
   - Measures coating thickness using eddy currents.

Soft Tubes

7. **Coating Continuity (Porosity) Test – Sodium Chloride and Copper Sulfate Test for Soft Tubes**
   - Similar to the sodium chloride and copper sulfate test for canisters.

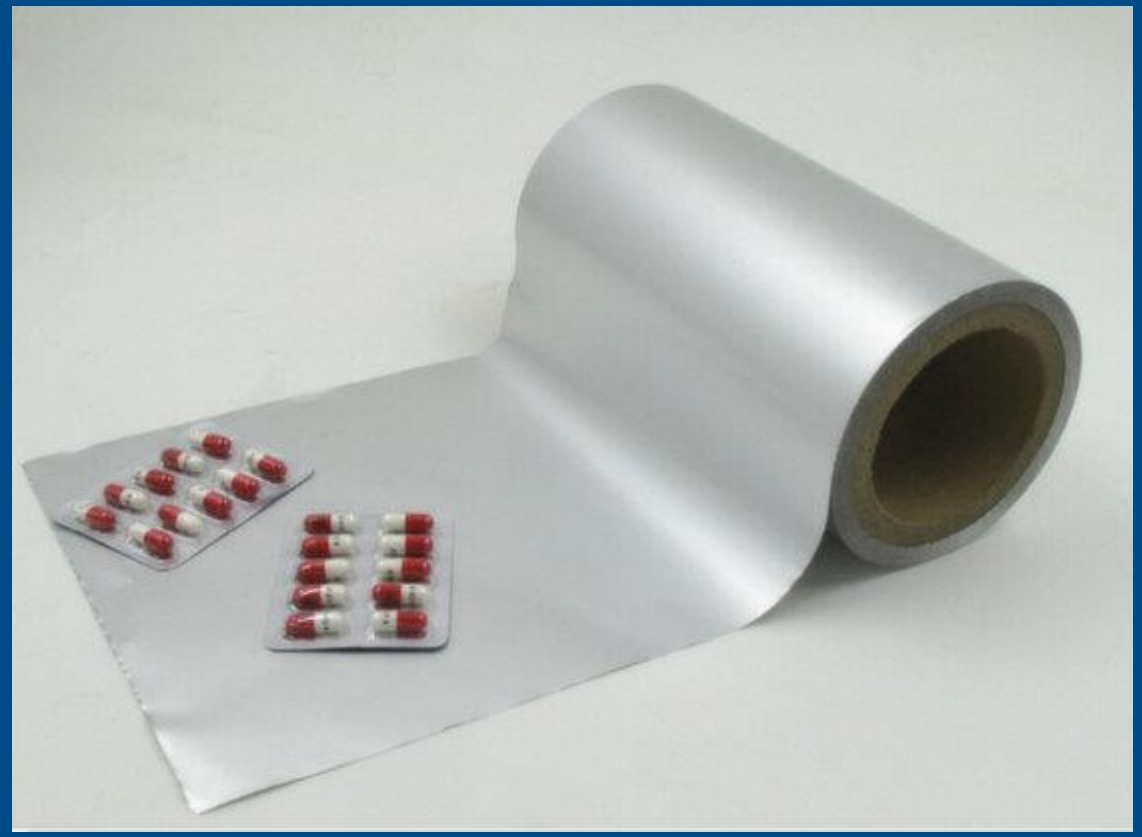
- **Purpose:** Examine the completeness, thickness, and durability of the coatings
- **Importance**: Ensures coatings are complete, durable, and effective in protecting the drug product

Functionality Tests

Tube Air Tightness and Deformation Tests

- **Purpose:** Ensures aluminum soft tubes maintain integrity
- Air Tightness Test
  - **Procedure**: Immerse sealed tubes in water and apply air pressure
  - **Detection**: Look for bubbles indicating leaks
- Tube Deformation Test
  - **Procedure**: Use a guillotine to cut the tube and measure deformation
  - **Purpose**: Assesses resistance to deformation
- **Importance:** Prevents contamination or leakage of drug product

Functionality Tests



Foil Pinholes in Pharmaceutical Packaging

- **Purpose**: Ensures aluminum foil's barrier properties are uncompromised
- **Test Procedure**
  - **Inspection**: Examine foil under a light table
  - **Measurement**: Count and measure pinholes
- **Specifications**
  - **Maximum Allowable Pinholes**:
    - **Example**: For 6 µm thick foil, up to 100 pinholes per square meter
- **Importance**: Ensures effective protection against environmental contaminants

Functionality Tests

Table 1. Functional Tests for Coated Aluminum Inhalation Canisters, Aerosol Cans, Soft Tubes and Foil, and Uncoated Aluminum and Stainless Steel Inhalation Canisters

Test Parameter	Coated Aluminum Inhalation Canisters and Aerosol Cans	Uncoated Aluminum and Stainless Steel Inhalation Canisters	Coated Aluminum Soft Tubes and Aluminum Foil
Burst Pressure	X	X	—
Particulate Matter	X	X	X
Surface Coatings	X	—	X
Tube Air Tightness	—	—	X[a]
Tube Deformation (Guillotine Test)	—	—	X[a]
Pinholes	—	—	X[b]

[a]Soft Tubes
[b]Foil

Chemical Analysis Tests

Solvent-Mediated Extraction

- **Purpose**: Evaluate potential extractables from metallic packaging
- **Test Procedure**
  - **Exposure**: Packaging materials are exposed to solvents such as ethyl alcohol or n-hexane
  - **Analysis**: Extracts are analyzed for Total Organic Carbon (TOC) or Non-Volatile Residue (NVR)
  - **Example**: Aluminum canisters are filled with solvent, sealed, incubated, and analyzed
- **Importance**: Ensures packaging does not leach harmful substances into the drug product

Thermal Extraction

- **Purpose**: Evaluate volatile organic extractables from packaging materials
- **Test Procedure**
  - **Heating**: Sample of packaging material is heated in a headspace autosampler vial
  - **Analysis**: Evolved gases are analyzed using gas chromatography-mass spectrometry (GC-MS)
  - **Example**: Coated aluminum packaging tested for volatile organic compounds at 80°C for 40 minutes
- **Importance**: Ensures packaging materials do not release volatile substances that could contaminate the drug product

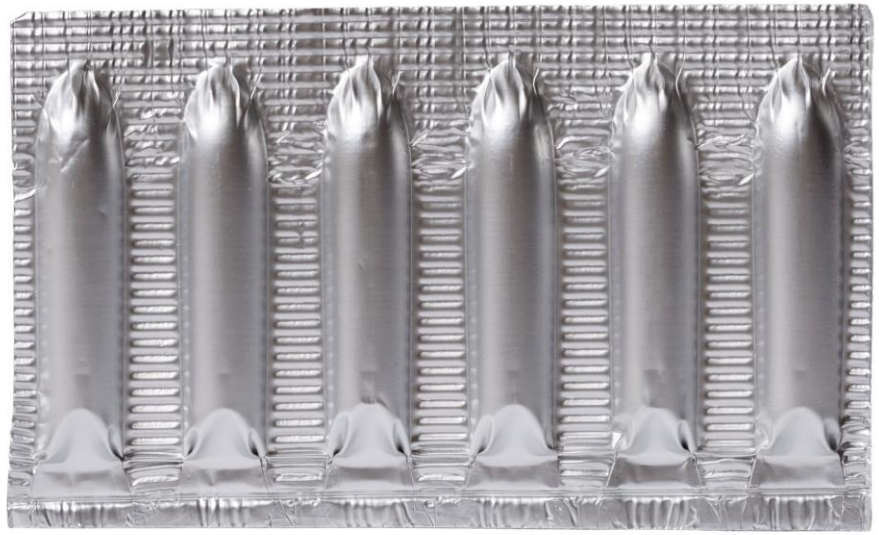
Extractables and Leachables: Regulatory Expectations

Regulatory Guidelines

- **Guidance**: Outlined in Chapter <662> and ICH Q3D(R2) for elemental impurities
- **Testing Methods**
  - **Analysis Techniques**: Use of Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) or Mass Spectrometry (ICP-MS)
  - **Purpose**: Analyze extracted elements from packaging materials

Safety Assessment

- **Comparison**: Results are compared against Permitted Daily Exposure (PDE) values.
- **Example**
  - **Inhalation Canisters**: Tested for elements like arsenic, cadmium, and lead
  - **Acceptable Limit**: 30% of PDE



<1662>: Materials and Manufacturing Processes for Metallic Packaging Systems

Chapter <1662>: Purpose

- **Support for Chapter <662>**: Chapter <1662> provides foundational information for understanding and evaluating the metallic packaging systems
- **Materials Specification**
  - **Aluminum Alloys:**
    - **1050A**: Known for its high purity and excellent corrosion resistance. Commonly used in inhalation canisters and aerosol cans.
    - **5052**: Provides superior strength and is highly resistant to corrosion. Ideal for use in canisters and other packaging requiring higher durability.
    - Foils:
      - Soft: 1100, 1200, 1235, 8011, 8021, and 8079
      - Hard: 1200-H18
  - **Stainless Steel Alloys:**
    - **316L**: Contains chromium, nickel, and molybdenum. Provides enhanced strength and resistance to corrosion, particularly useful in canisters and other components requiring durability and protection against harsh environments.

Materials and Manufacturing Processes

Key Focus Areas

1. **Materials**
   - **Aluminum Alloys**
     - **Elemental Composition**: Specific alloys used in pharmaceutical packaging
   - **Stainless Steel Alloys**:
     - **316L**: Contains chromium, nickel, and molybdenum
     - **Properties**: Enhanced strength and corrosion resistance
2. **Manufacturing Processes**
   - **Types of Packaging**
     - Canisters
     - Aerosol Cans
     - Soft Tubes
     - Foil
   - **Surface Coatings**

Manufacturing Processes: Stainless Steel and Aluminum

Stainless Steel Canisters

- **Formation**
  - **Techniques**: Deep drawing or impact extrusion
- **Post-Formation**
  - **Cleaning**: Removes contaminants
  - **Coatings**: Internal and external coatings prevent chemical reactions and enhance durability

Aluminum Canisters and Aerosol Cans

- **Formation**
  - **Techniques**: Deep drawing or impact extrusion
- **Multi-Step Process**
  - **Shaping**: Forming into the desired shape
  - **Washing**: Cleans the surface
  - **Drying**: Removes moisture
  - **Coating**: Applies protective layers
  - **Curing**: Hardens coatings
  - **Printing**: Adds labels or markings

Soft Tubes

- **Manufacturing**
  - **Similar Steps**: Formation, cleaning, coating, and curing to ensure quality and protection

Coating Techniques and Importance

Coating Techniques

- **Internal Coatings**
  - **Fluorinated Ethylene Propylene (FEP)**
  - **Epoxy Phenolic Lacquer**
- **Application Methods**
  - **Spraying**: Uniform application of coatings
  - **Electrostatic Powder Coating**: Ensures even coverage
  - **Gas Plasma Processing**: Produces a thin, uniform coating with enhanced barrier properties

Importance of Coatings

- **Protection**
  - **Prevents Contact**: Keeps drug product from interacting with metal
  - **Minimizes Drug Deposition**: Reduces residue on container walls
- **Quality Assurance**
  - **Prevents Contamination**: Maintains the integrity of the pharmaceutical product
  - **Enhances Barrier Properties**: Ensures effective protection

Summary

Chapter <662> Metallic Packaging Systems and Their Materials and Components of Construction

- **Objective**
  - Characterizes and tests metal materials and components used in pharmaceutical packaging
- **Key Testing Procedures**
  - Burst Pressure Test
  - Particulate Matter Test
  - Surface Coatings
  - Tube Air Tightness and Deformation
  - Foil Pinholes
  - Solvent Mediated Extractions
  - Thermal Extraction

Chapter <1662> Materials and Manufacturing Processes for Metallic Packaging Systems

- **Material Composition**: Discusses aluminum and stainless-steel alloys and their applications
- **Manufacturing Processes**: Describes forming, coating, and final processing of metal packaging components
- **Coating Techniques**
  - Internal Coatings: Includes FEP and epoxy phenolic lacquer
  - Application Methods: Spraying, electrostatic powder coating, and gas plasma processing

Thank You

The standard of trust