Drug Product Quality and the Impact of Extractables and Leachables

Diane Paskiet, MS
Senior Director, Global Scientific Affairs
West Pharmaceutical Services, Inc.
November 8, 2017
Objective

- Leachables and Extractables (L&E) Expectations
- Leachable Impact to Drug/Biologic Product Quality and Patient Safety
- Implementing Risk Management Strategies
- L&E Guidance and Recommendations
Extractables and Leachables (L&E) Expectations

- Generics : QbR Deficiencies
  - Container closure attributes to ensure product quality
  - Studies to identify necessary attributes including identity, suitability (safety, protection, compatibility, and performance) consistent with the QTPP
  - Dosage form compatibility (e.g. extractables, leachables, dye from labeling)
  - Compatibility with the sterilization procedure
  - Validated Functional barrier to microbial ingress
  - Performance system (e.g. dropper consistency, calibration of delivery device)

Continued need to focus on efficient and science-based decision-making
Increased focus on product and process understanding

Robert Iser, Acting Division Director, Chemistry, FDA OGD

Janet Woodcock CPHA May, 2016
2016 Scientific, Regulatory and Quality Conference
Linking Extractables to Leachables and Patient Safety

Extractables

- Extractable Size/Shape
- Total Concentration
- Exposure Area
- Diffusion-Thickness
- Time-Temperature

Dependencies

- Drug Product Extraction Propensity
- Contact Area
- Extractable Solubility
- Extractable Interactions

Correlations

- Product Quality/Safety
- Compatible Systems
- Delivery Performance
- Product Quality Protection

Safe and Effective Delivery
GMP Requirements
Code of Federal Regulation (CFR)

- **Finished Drug Product: Containers and Closures**
  Device containers should not be reactive, additive or absorptive as to alter the safety, identity strength, quality or purity of the drug... 21CFR 211.94
  Laboratory Controls shall include scientifically sound and specifications, standards, sampling plans, test procedures, re-sampling, retesting, and data interpretation ... 21 CFR 211.160

- **Biologics: Equipment, Containers and Closures**
  All surfaces that come in contact with products shall be clean and free of surface solids, leachable contaminants...... 21 CFR 600.11(b) (h)
## Regulatory Landscape

<table>
<thead>
<tr>
<th>Drugs 21CFR300</th>
<th>Biologics 21CFR600</th>
<th>Devices 21CFR800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Molecules (generally synthetic)</td>
<td>Large Molecules (living organisms)</td>
<td>Devices (technology)</td>
</tr>
<tr>
<td>Analytically well defined and stable</td>
<td>Analytically complex and unstable: vaccines, gene therapy, tissue, blood, cellular products</td>
<td>Engineered to meet specific inputs: catheters, prosthetics, in-vitro diagnostics</td>
</tr>
</tbody>
</table>

### Regulatory Pathway

- Component Sterilization-Processing-Manufacturing
- Container Closure/Delivery Systems (CCS) Storage and Shelf Life Stability

### Combination Products
- Drug + Device
- Drug + Biologic
- Biologic + Device

21CFR 4
FDA L&E Guidance Degree of Testing Drugs vs Devices

**Degree of Concern Associated with the Route of Administration**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Likelihood of Packaging Component Dosage Form Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Highest</td>
</tr>
<tr>
<td>a) aerosols</td>
<td>High</td>
</tr>
<tr>
<td>b) Injections</td>
<td></td>
</tr>
<tr>
<td>c) Sterile powders</td>
<td></td>
</tr>
<tr>
<td>d) injection and inhalation</td>
<td></td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>High</td>
</tr>
<tr>
<td>a) solutions</td>
<td></td>
</tr>
<tr>
<td>b) nasal aerosols</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Low</td>
</tr>
<tr>
<td>a) solutions</td>
<td></td>
</tr>
<tr>
<td>b) lingual aerosols</td>
<td></td>
</tr>
<tr>
<td>c) Oral solutions</td>
<td></td>
</tr>
<tr>
<td>Oral powders</td>
<td></td>
</tr>
<tr>
<td>c) capsules</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviated Information**

**Medical Device Categorization**

<table>
<thead>
<tr>
<th>Medical Effect</th>
<th>Nature of Body Contact</th>
<th>Contact Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue/Bone/Dentin</td>
<td>A - Limited</td>
<td>&lt;24 h</td>
</tr>
<tr>
<td>Circulating Blood</td>
<td>B - Prolonged</td>
<td>&lt;24 h-30 d</td>
</tr>
<tr>
<td>Systemic Tox</td>
<td>C - Permanent</td>
<td>&gt;30 d</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitize/Irritate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemocompatibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute/chronic Tox</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repro/Dev Tox</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degradation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Extractables Data Should Encompass System Performance and Compatibility Linked to Product Attributes**

**Leachables Depends on Risk to Migration in (Drug/Biologic/Body Contact) In Use**

**Safety is Linked to Patient Daily Exposure and Quality is Linked to Drug Product Attributes**

**Degree of Testing Depends on Multiple Components of Final System (Primary/Secondary/Tertiary)**

**Container Closure Systems for Packaging Human Drugs and Biologics CMC Documentation**

10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"
Defining the L&E Strategy

**Device**

820 Quality Systems Regulation*
- 820.20 (management)
- 820.30 (design)
- 820.50 (purchasing)
- 820.100 (CAPA)
- 820.170 (installation)
- 820.200 (servicing)

Called out sections*

**Drugs**

211 Finished Pharmaceuticals*
- 211.84 (incoming testing)
- 211.103 (calc of yield)
- 211.137 (esp. dating)
- 211.165 (release testing)
- 211.166 (stability testing)
- 211.167 (special testing)
- 211.170 (reserve samples)

A biosimilar product in a delivery device **Combination Product** may require a separate application for the device

FDA Biosimilars: Generics Q & A
Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
Leachable Impact to Drug/Biologic Product Quality and Patient Safety

L&E Risk-Based Approaches Include Chemical & Biocompatibility

CDRH (ISO 10993-1) – Device
  - **Residuals or impurities**
    - Alter the biological response
    - Change the device surface properties
      - Consider amount of chemical in device/device extracts (ug/device or ug/patient)
    - Consider all biocompatibility relevant endpoints for duration & use

CDER/CBER- Container Closure Systems
  - **L&E**
    - Toxicant, irritant, sensitizer interaction products
      - Consider amount of chemical (ug/containment system)
    - Assess safety compared to a total daily intake
    - Consider impact to product quality and toxicity of leachables
L&E Challenges Drug vs Biologics

Small Molecules
Chemically Synthesized
- Structures established
- Fixed Manufacturing
- Large Batch size
- Single Active Typical

Large Molecules
Living Cell/Organisms
- Characterization
  - May not be completely defined
  - Often RT unstable
- Complex Manufacturing
- Small batch size
- Potential more than a single active

The nature and complexity of biologic products are multifaceted
Biologic quality depends on the level of biologic product characterization
Impurities Assessment
ICH Guidelines

- Impurities Drug Products/Substances Applies To: (Q3A/B)
  - **Degradation** products or **reaction** products of the drug substance with immediate container closure system

- Impurities Biologics (Q6B)
  - **Product-related substances**: Molecular variants of the desired product formed during manufacture and/or storage
    - Occurs over time and/or by light, temperature, pH, water
    - Or by reaction with an excipient and/or the immediate container/closure system.

Drug product quality stability, purity, efficacy
Comparability Assessments: Components/Systems

Changes to multiple components of a container closure system should adequately address the potential effects of component interchangeability on product quality.

**Component Compliance**
- Product Quality and Safety
- Compatibility and Interactions

**System Qualification**
- Protection
- Function
- Performance

Product is Process Understanding
## Integration of Drug Product Development with L&E

<table>
<thead>
<tr>
<th>Development</th>
<th>Technology Transfer</th>
<th>Commercial Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Product Profile (TPP)</strong></td>
<td><strong>CCS/Device Selection</strong></td>
<td><strong>Leachable Verification</strong></td>
</tr>
<tr>
<td><strong>Admin Route</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Prior Knowledge</td>
<td>Potential Leachables</td>
</tr>
<tr>
<td>Concentration</td>
<td>Material Compliance</td>
<td>Method Dev/Validation</td>
</tr>
<tr>
<td>Dosing//Frequency</td>
<td>System Compatibility</td>
<td>Shelf-Life Study</td>
</tr>
<tr>
<td>Formulation</td>
<td>Performance/Function</td>
<td></td>
</tr>
<tr>
<td>Shelf Life</td>
<td>Extractable Profiles</td>
<td>Confirm Leachables</td>
</tr>
<tr>
<td></td>
<td>Hazard Assessment</td>
<td>Safety Assessment</td>
</tr>
<tr>
<td></td>
<td>Target Leachables</td>
<td>CCS/Device Correlation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitigation/Control</td>
</tr>
</tbody>
</table>

### CCS/Device Selection
- Prior Knowledge
  - Material Compliance
  - System Compatibility
  - Performance/Function
- Extractable Profiles
  - Hazard Assessment
  - Target Leachables

### Leachable Verification
- Potential Leachables
  - Method Dev/Validation
  - Shelf-Life Study
- Confirm Leachables
  - Safety Assessment
  - CCS/Device Correlation
  - Mitigation/Control

- Yes: L/E Control Strategy
- No: Risk Review
- Change Management
- Lifecycle Management
- Continuous Improvement
Implementing Risk Management Strategies

- ICH 8: Pharmaceutical Development
- ICHQ9: Quality Risk Management
- ICH Q10 Quality Systems Management
- ICH Q12 Lifecycle Management

Image Quality Risk Management Background ICH Q9 EWG Training July 2006 [www.ICH.org](http://www.ICH.org)
ICH Q9 Applied to L&E Management

Leachable
Severity
Extractable Hazard
Probability
Detectability

Image adapted from Quality Risk Management Background ICH Q9 EWG Training July 2006 www.ICH.org
Risk Communications: L&E Terminology

Extractable Profiles

Material Characterization
- Extractables
- Material Understanding
- Potential Extractable
- Potential Leachable

Simulation Study
- Worst Case
- Accelerated Leaching
- Migration
- Probable Leachable
- Predicted Leachable

Drug Product Leachable

Leachables
- Leachate
- Product-related impurity
- Process-related impurity
- Migrant
- Contaminant

Risk Assessment
- Potential Hazard
- Hazard ID
- Hazard Assessment
- Safety Assessment
- Toxicology Assessment
- Toxic Dose
L&E Severity

- **Leachables Consequence**
  - Patient Harm
    - Toxicity, immunogenicity
  - Loss of Efficacy
    - Product interaction, loss of activity; biologic modification
  - Poor Quality
    - Product stability, impurities

- **Extractables Significance**
  - Identification of Hazards
    - Toxic and/or nontoxic chemical entities
  - Material Understanding
    - Potential for migration and indication of performance properties
  - **System Compatibility** (Storage-Delivery)
    - Delineates functional properties
Extractable Hazard: Impact to Product Quality

Components/System Compatibility

- Packaging components will not interact to cause unacceptable changes in the quality of dosage form or the packaging component.
- Original application, a supplemental application, or as fulfillment of a commitment to conduct post-approval stability studies.

- Loss of potency due to absorption or adsorption of the active drug substance
- Degradation of the active drug substance induced by leaching
- Reduction in the concentration of an excipient
- Precipitation, changes in drug pH
- Discoloration of either the dosage form or the packaging component
- **Interactions between a packaging component and dosage form can be detected during qualification studies on the container closure system or in the stability studies.**
Extractable Hazard: Potential Impact to Bioequivalence

Extractable Forms the Basis of Suitability for Use

- **Material Chemical Characterization/Understanding**
  - Delivery Performance – Affecting Dose
  - ID Critical Component/System Attributes
  - Essential part of assessing effects of potential material changes

- **Material Compatibility**
  - Drug Product Degradation; Interaction
  - Loss of Potency; Stability
  - Product/Excipients Surface Interaction (adsorbing/absorbing)

- **Extractable Simulation Studies**
  - Likely Migrants and Concentration
  - Potential Toxicity and Reactive Species
Probability: Patient Harm

Change in Eprex formulation resulted in leachable that was a probable cause of immunogenicity.

PRCA cases coincides with PS 80 uncoated stoppers.
Probability: Biologics Quality

- **Visible particulates**: elements leached from glass
  - Leached aluminum + sodium phosphate buffer
  - Leached barium + sodium sulfate buffer

- **Drug product degradation**: element leached from rubber
  - Leached aluminum catalyzed bisulfite reaction

- **Protein aggregation**
  - Tungsten oxide leached anion from process to insert needle into glass barrel

\[ \text{WO}_3 \rightarrow \text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O} \]


J.S. Bee et al Precipitation of monoclonal antibody by soluble tungsten Journal of Pharmaceutical Sciences 98((9),3290-3301
Probability: Predicted Migration

- Polycarbonate Container
- Extractable Profiles IPA/Water; pH 2.5 and 9.5
Probability: Predicted Migration

Migration Label Adhesive Through A Semi-Permeable Container

Simulated Leaching (Migration) Study for a Model Container-Closure System Applicable to Parenteral and Ophthalmic Drug Products; PDA Journal of Science and Technology, 2017
Detectability: Leachables Challenges

- Leachables can be masked or suppressed
- Target potential leachables studies are necessary
- Migration kinetics (leaching) are generally slow
- Interaction of leachable with drug/biologic product can occur
- Accelerated and real-time leachable stability data is needed to confirm leachables*
- Identification of interaction products is relative to drug/biologic characterization
- Confirmed leachables should be correlated to extractable profiles to enable control

Extractable Profiles are needed to guide leachable risks

*FDA Guidance on Immunogenicity Assessment for Therapeutic Protein Products*
## L&E Guidance and Recommendations

<table>
<thead>
<tr>
<th>Evaluations</th>
<th>PQRI Recommendations &amp; Demonstration</th>
<th>USP Methods + Guidance</th>
<th>ISO 10993 Methods</th>
<th>Ph.Eur Methods + Basic Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specifications</strong> (Starting Point)</td>
<td>Risk Based Justifications No specs</td>
<td>Plastic Elastomers Glass</td>
<td>Plastics Elastomers Glass</td>
<td>Plastics Elastomers Glass</td>
</tr>
<tr>
<td><strong>Extractable Assessments</strong> (Hazard ID)</td>
<td>Inhaled &amp; Parenteral Products Characterize, Simulate, Control Correlation to CCS</td>
<td>&lt;1663&gt; PQRI Aligned</td>
<td>ISO 10993 Extraction Part 12-Exhaustive Part -18 Simulated</td>
<td>EMA Plastic Guideline Extractions</td>
</tr>
<tr>
<td><strong>Leachable Assessments</strong></td>
<td>Based on Extractable data and potential for Interaction</td>
<td>&lt;1664&gt; PQRI Aligned</td>
<td>ISO 10993 Part 17</td>
<td>EMA Plastic Guideline Migrate/Interact</td>
</tr>
<tr>
<td><strong>Safety Assessments</strong></td>
<td>Correlation to CCS and drug/biologic product Safety ID Thresholds Strategies based on risk to patient</td>
<td>Plastic &amp; Elastomers Endpoints Cytotoxicity Irritation Sensitization Implantation Systemic Tox Subchronic Tox</td>
<td>ISO 10993 Med Devices USP End Points + Genotoxicity Hemocompatibility Carcinogenicity Reproductive/Dev Developmental Tox</td>
<td>EMA Plastic Guideline Tox Documentation</td>
</tr>
</tbody>
</table>

Extractable and Safety Tests Vary by Extraction/Conditions
USP Relevant L&E Chapters

Glass Containers
- 1660
- 660

Elastomers Components
- 1381
- 381
- 1382
- 382

Plastics Materials
- 1661
- 661

Polymer Manufacturing Components
- 1665
- 665

L&E
- 1663
- 1664
- 87
- 88
- 1031

Chapters > 1000 Informational; Chapters < 1000 Specifications
USP Testing is a Starting Point to Qualify for Use
PQRI Finding Leachables: The Forest Through the Trees
Safety Concern Threshold (SCT)
- Low Risk Leachables Not Identified
  - <0.15 μg/day

Qualification Threshold (QT)
- Assessment of Identified Leachable
  - Non-carcinogenic >5 μg/day

Best Practices for E&L studies
- Controlled Extraction Studies (CES)
  - Analytical Evaluation Threshold (AET)
    - Identification threshold

Note:
- **Designed to reduce level of uncertainty within the pharmaceutical development**
- **Not meant to be prescriptive**

Application to Parenteral Drug Products to be Released Soon
## PQRI Risked-Based Approaches for L&E Testing

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Key Characteristics</th>
</tr>
</thead>
</table>
| **Material Characterization** (Tentative Leachables) | - Screening of packaging candidates  
- Establish composition of extractable materials  
- Broad Based/Screening extraction and testing protocols  
- Semi-quantitative character  
- **Toxicological Alerts** |
| **Simulation Study** (Probable Leachables) | - Establish worst case accumulation of leachables  
- Conditions to mimic worst case Exposure (accelerated)  
- Justified simulating solvents  
- Assessment of all extractables above the AET  
- **Identify Leachable Targets** |
| **Migration Study** (Confirmed Leachables) | - Establish the actual accumulation of target leachables  
- Drug product under actual conditions of use  
- **Toxicological assessment of all targeted leachables**  
Outcome: Negligible or unacceptable safety risk |

### Best Demonstrated Practices
- **Analytical Techniques:**  
  - Multiple and Orthogonal  
  - Quantitative  
  - Compound Specific  
  - Sensitive

### Extraction Considerations:
- Polar/nonpolar  
- Aqueous/Ionic  
- Co-solvents

### Detection of:
- Organic  
- Volatile  
- Semi volatile  
- Non volatile  
- Inorganic

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Extractables Characterization for Five Materials of Construction Representative of Packaging Systems used for Parenteral and Ophthalmic Drug Products; PDA Journal of Science and Technology 2013
## PQRI Parental Drug Products Recommendations

### Proposed Thresholds

<table>
<thead>
<tr>
<th>Proposal</th>
<th>Class I No Genotox</th>
<th>Class II No Genotox</th>
<th>Class III Genotox M7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (μg/day)</td>
<td>50 If Systemic</td>
<td>5 If Irritant/Sensitizer</td>
<td>1.5 To Identify</td>
</tr>
</tbody>
</table>

### Best Practices

<table>
<thead>
<tr>
<th>Characterization</th>
<th>Simulation</th>
<th>Leachables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material Chemistry</td>
<td>Mimic Actual Use</td>
<td>Actual Drug Product</td>
</tr>
</tbody>
</table>

### LVP, SVP, PFS Applications

- Considerations Given
- Ophthalmics
- Biologics
Assessing L&E Risk: PQRI and USP Alignment

- Identify Extractable Risk/Uncertainty
  - A \cong B

- Patient Contact Dosage Form Surface Interfaces
  - \[ r = k[A]^x[B]^y \]

- Characterize Materials

- Simulate Components

- Simulate Systems

- Correlate
L&E Uncertainty-Residual Risk

• **Materials Understanding**
  Components – lot variability
  Systems – final process & product

• **Measurements**
  Extractions
  Analytical Techniques

• **Migration Kinetics**
  Exposure
  Conditions/Duration
Packaging Systems: Risk Analysis

Component selection should be based on sound and justifiable scientific principals and studies designed to address risk

1. To understand extractables for individual component and potential to migrate
2. To link chemistry with drug/biologic quality and performance/function of packaging
3. To assess safety and compatibility of components and systems
4. To understand impact of manufacturing, storage and shipping of the drug product
5. To correlate to clinical use and patient safety

Understand risk to safety associated with the packaging system with drug product
*Dose * Duration * Patient Population * Other Unique Product Attributes