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FallTech
Conference 2017

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

Robert Iser, Acting Division Director, Chemistry, FDA OGD

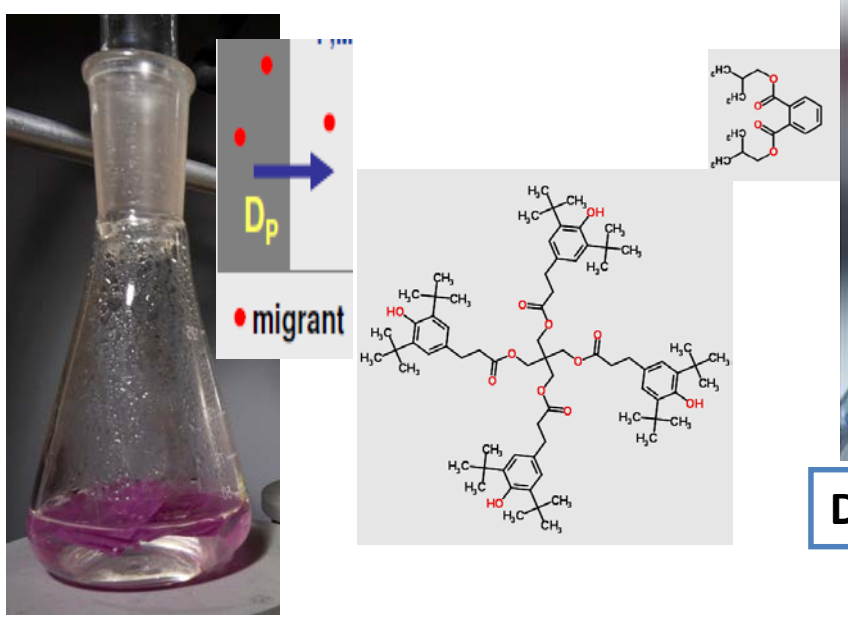
Continued need to focus on efficient and science-based decision-making

Increased focus on product and process understanding

Janet Woodcock CPHA May , 2016
2016 Scientific, Regulatory and Quality Conference

Linking Extractables to Leachables and Patient Safety

Extractables



Dependencies

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

Leachables

Dependencies

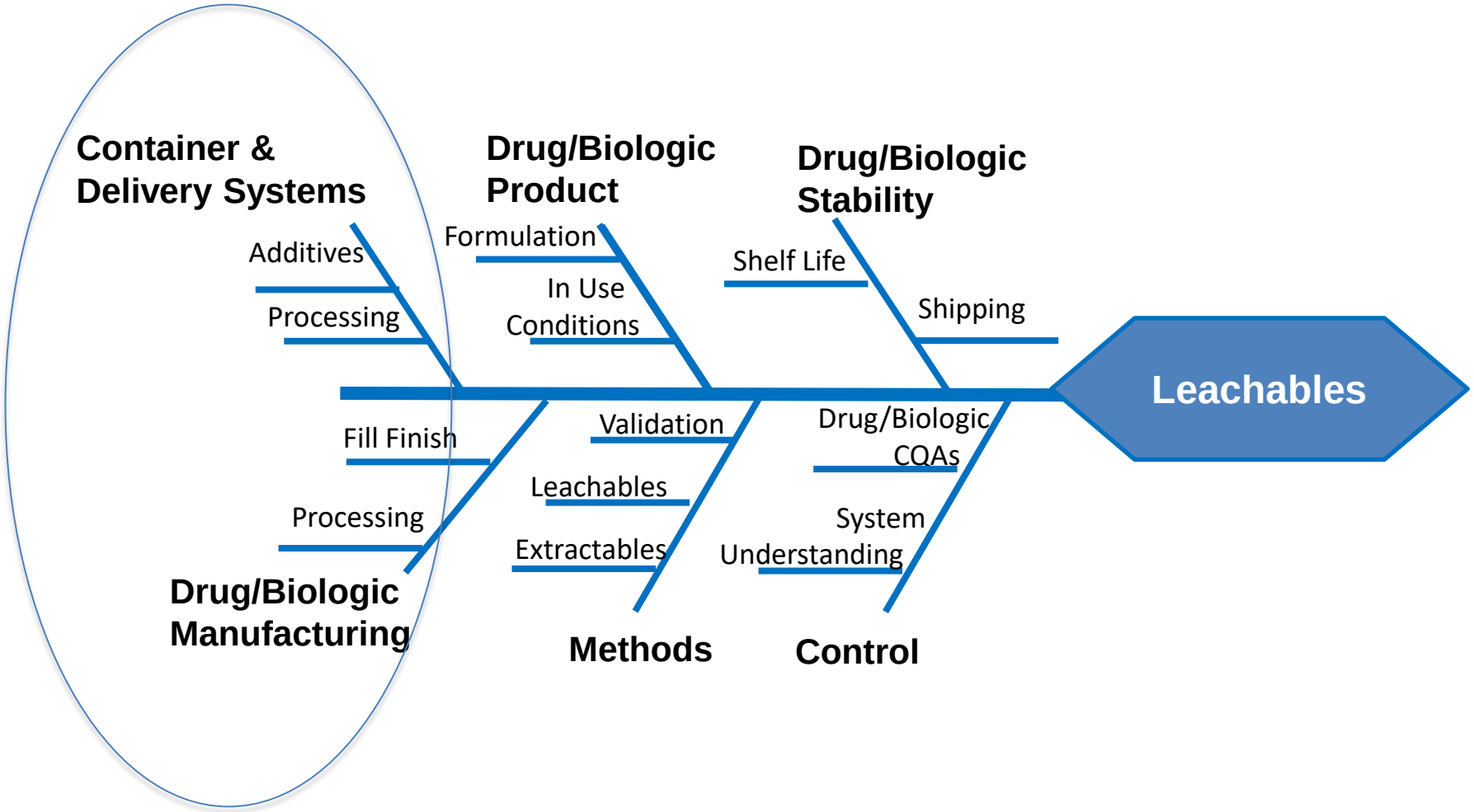
- Drug Product
- Extraction Propensity
- Contact Area
- Extractable Solubility
- Extractable
- Interactions

Safe and Effective Delivery

Correlations

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

Leachables Qualification Factors



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

Drugs 21CFR300 	Biologics 21CFR600 	Devices 21CFR800 
Small Molecules (generally synthetic)	Large Molecules (living organisms)	Devices (technology)
Analytically well defined and stable	Analytically complex and unstable: vaccines, gene therapy, tissue, blood, cellular products	Engineered to meet specific inputs: catheters, prosthetics, in-vitro diagnostics
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	Likelihood of Packaging Component Dosage Form Interaction		
	High	Medium	Low
	lingual aerosols Oral solutions	Oral powders	capsules
Abbreviated Information			

Container Closure Systems for Packaging Human Drugs and Biologics CMC Documentation

Medical Device Categorization			...ical Effect
Nature of Body Contact	Contact Duration		
Abbreviated Information			

10993-1, "Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process

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)

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

Defining the L&E Strategy

Inter-Center Collaborations

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

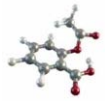
CDER/CBER- Container Closure Systems

- **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

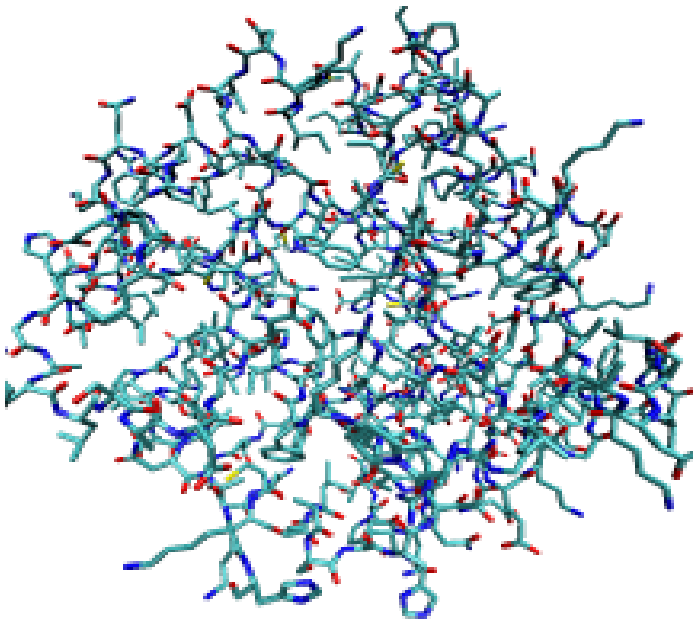
Small Molecules

Chemically Synthesized



21 atoms

- Structures established
- Fixed Manufacturing
- Large Batch size
- Singe Active Typical



Large Molecules

Living Cell/Organisms

25,000 atoms

- Characterization
  - May not be not 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

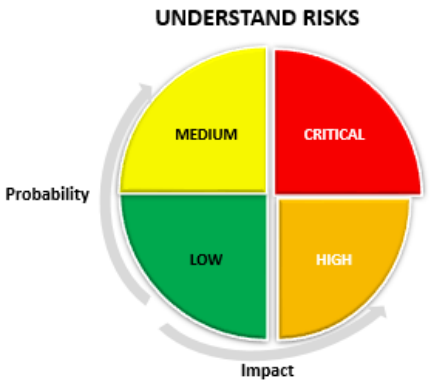
- Impurities Biologics (**Q6B)**
  - **Product-related substances:** Molecular variants of the desired product formed during manufacture and/or storage
    - Occurs over time and/or by light, temperature, pH, water
    - Or by reaction with an excipient and/or **the immediate container/closure system**.

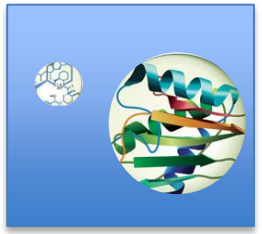
Drug product quality stability, purity, efficacy

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

Development | **Technology Transfer** | **Commercial Manufacturing**

Target Product Profile (TPP)

Admin Route
Dosage Form
Concentration
Dosing//Frequency
Formulation
Shelf Life

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

Implementing Risk Management Strategies

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

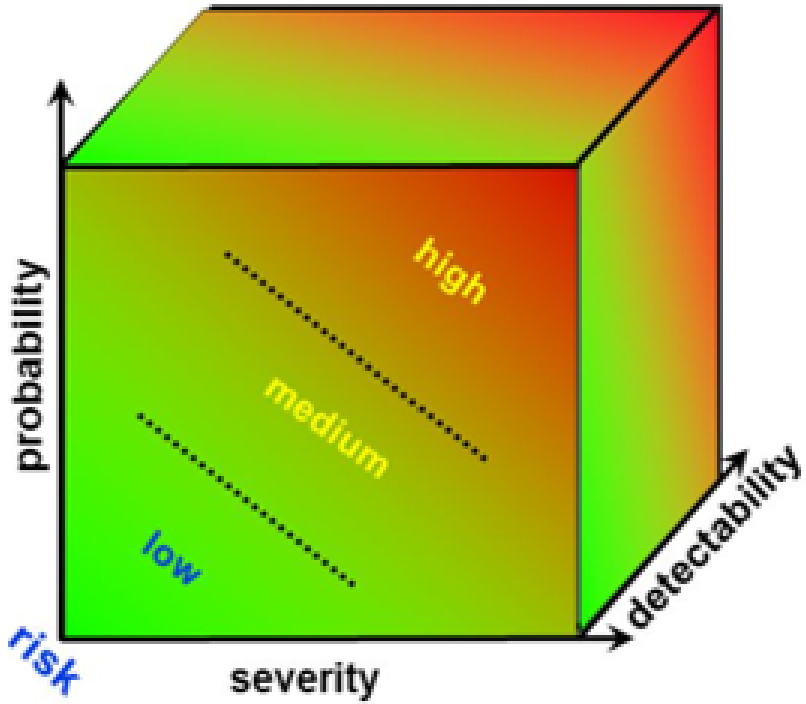
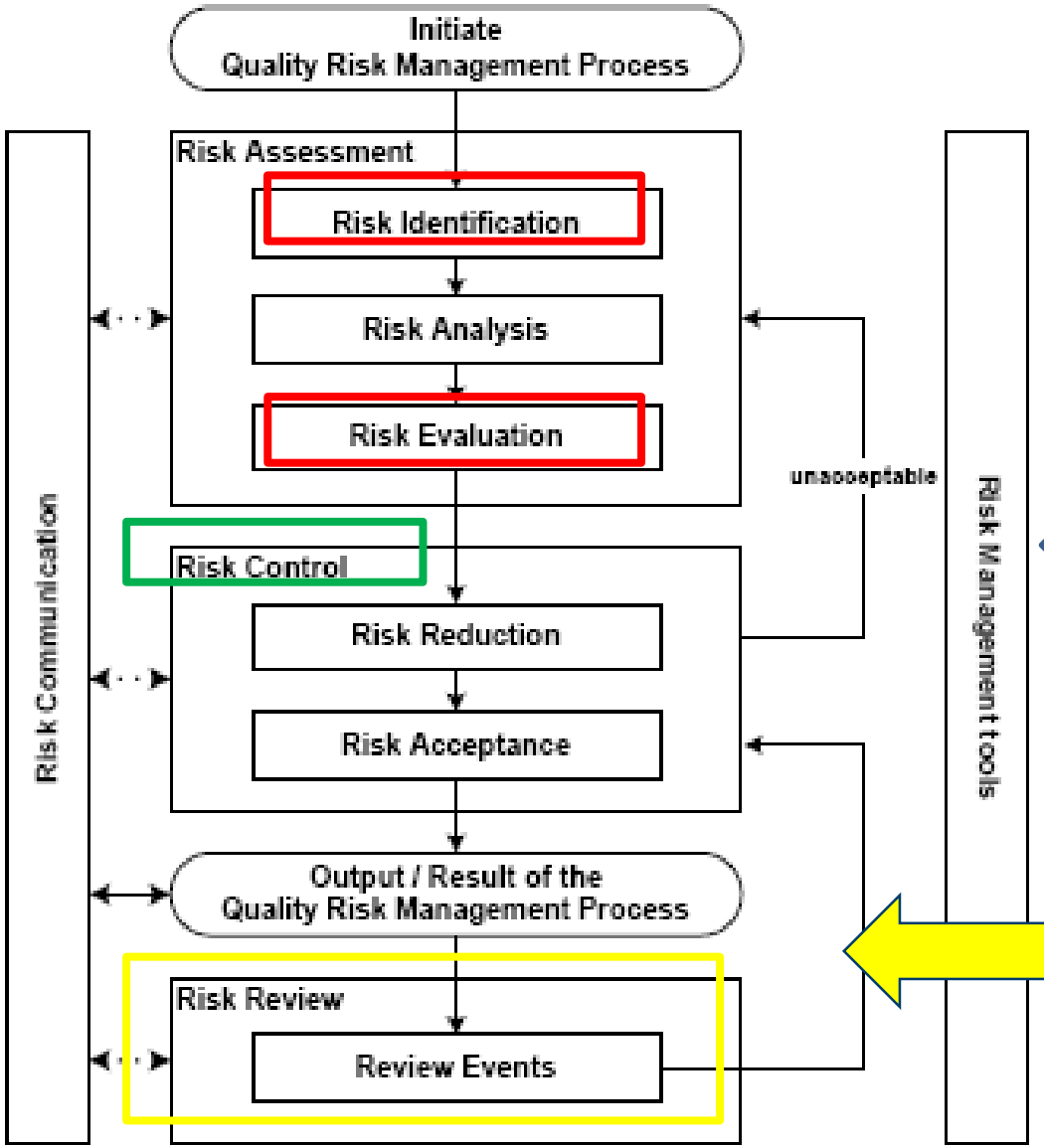


Image Quality Risk Management Background ICH Q9 EWG Training July 2006 www.ICH.org

ICH Q9 Applied to L&E Management

Leachable
Severity
Extractable Hazard
Probability
Detectability



Development

CQAs/CPPs

Continual Improvement

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.**

The FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, CDER/CBER 1999

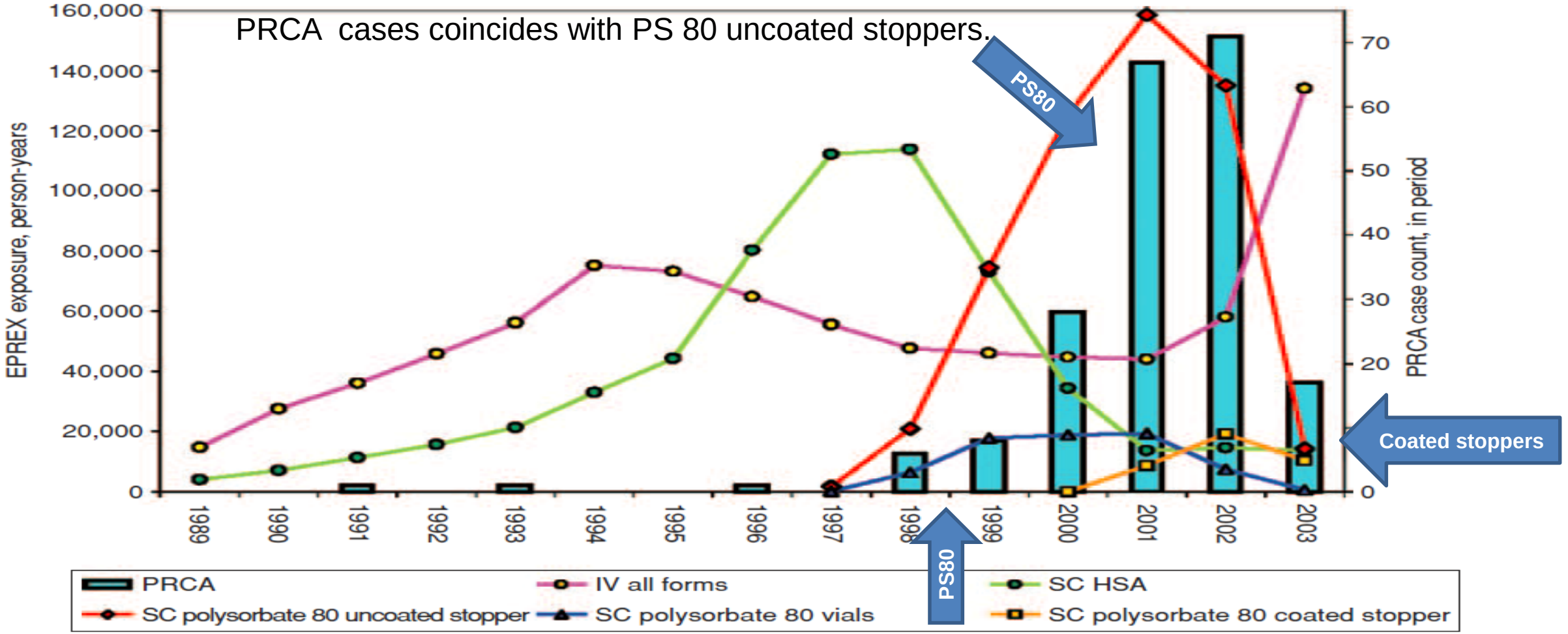
Extractable Hazard: Potential Impact to Bioequivalence

Extractable Forms the Basis of Suitability for Use

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

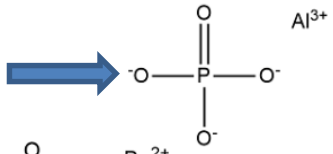
Change in Eprex formulation resulted in leachable that was a probable cause of immunogenicity



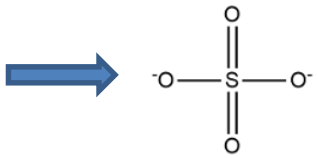
Katia Boven et.al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes; Kidney International, Vol. 67 (2005), pp. 2346–2353

Probability: Biologics Quality

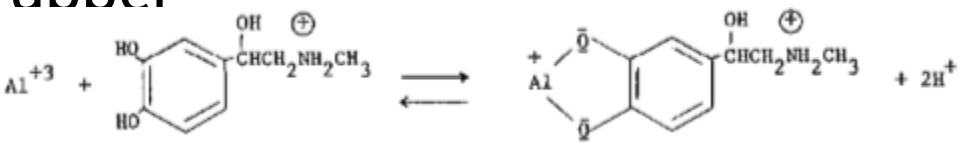
- **Visible particulates**: elements leached from glass
  - Leached aluminum + sodium phosphate buffer



  - Leached barium + sodium sulfate buffer



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



Al- Epinephrine Complex

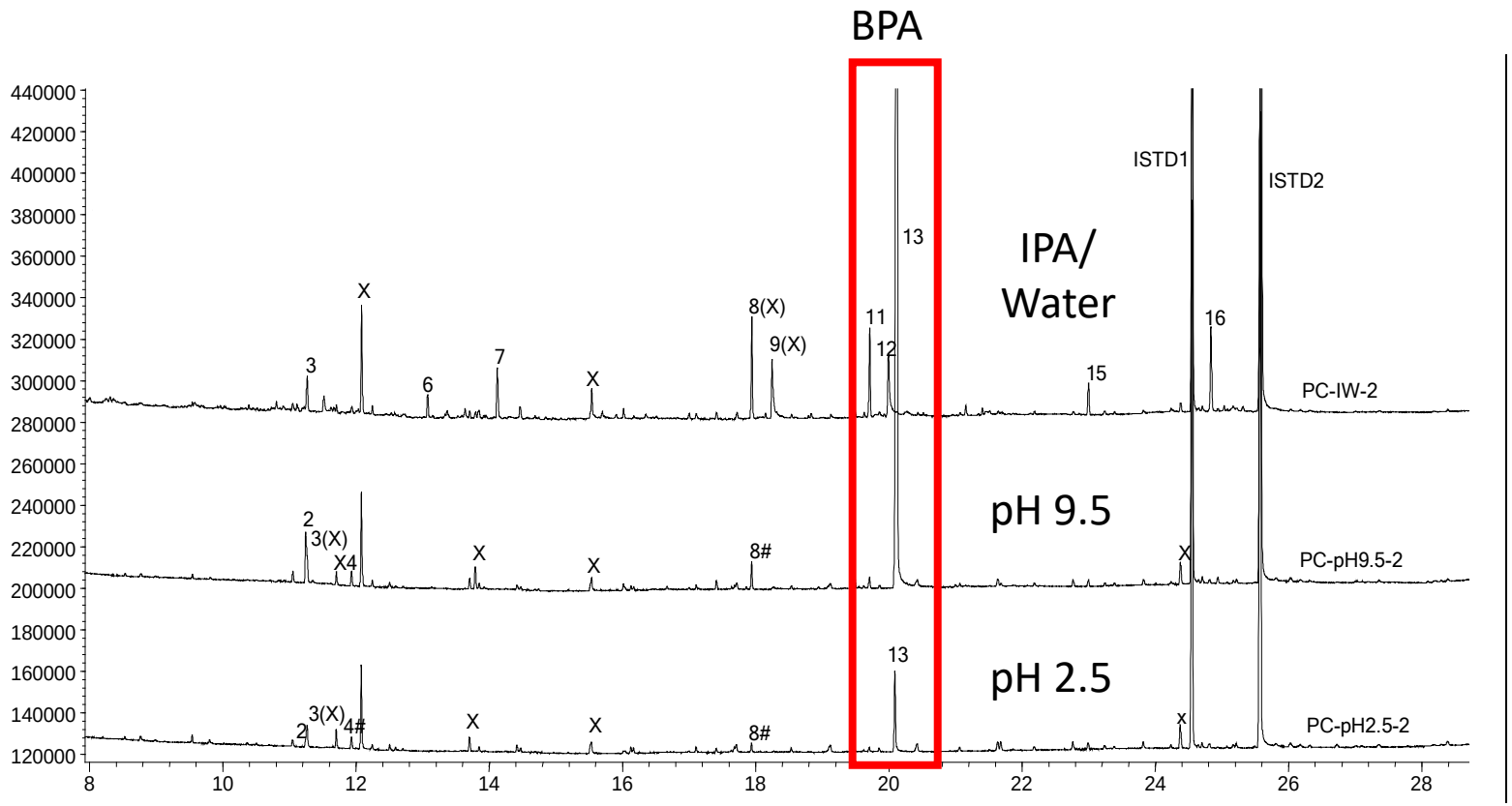
- **Protein aggregation**
  - Tungsten oxide leached anion from process to insert needle into glass barrel

$$WO_3 \rightarrow Na_2WO_4 \cdot 2H_2O$$

I. Markovic Risk Management Strategies for Safety Qualification of Extractables and Leachable Substances in Therapeutic Biologic Protein Products, American Pharmaceutical Review, 2009
E. Milano et.al The Formation of an Aluminum-Epinephrine Complex and Its Effect on the Addition of Bisulfite to Epinephrine, PDA Journal Sci-tech *vol. 37 no. 5 165169, 1983*
J.S. Bee et.al Precipitation of monoclonal antibody by soluble tungsten Journal of Pharmaceutical Sciences 98((9),3290-3301

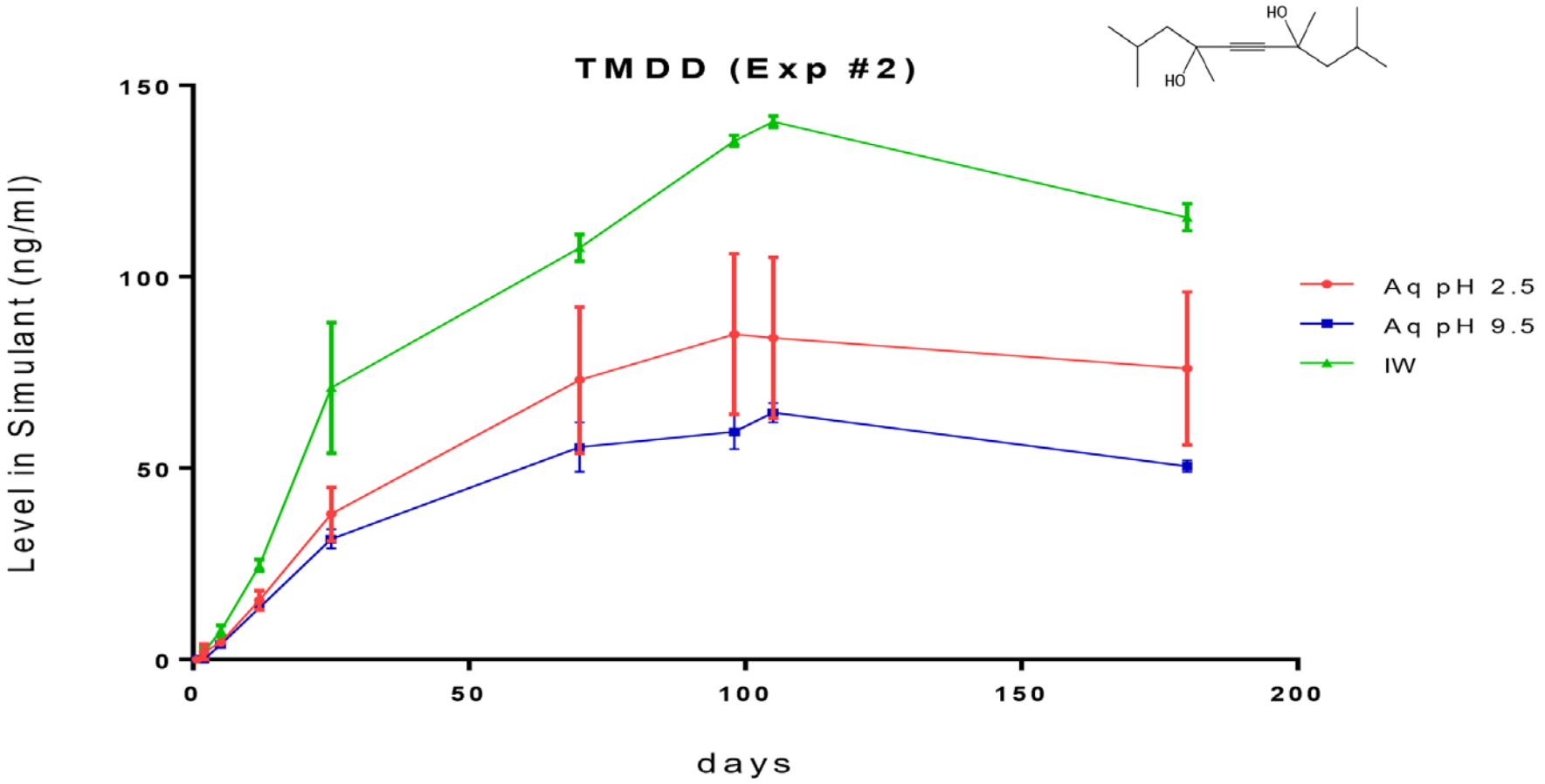
Probability: Predicted Migration

- 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 mask 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

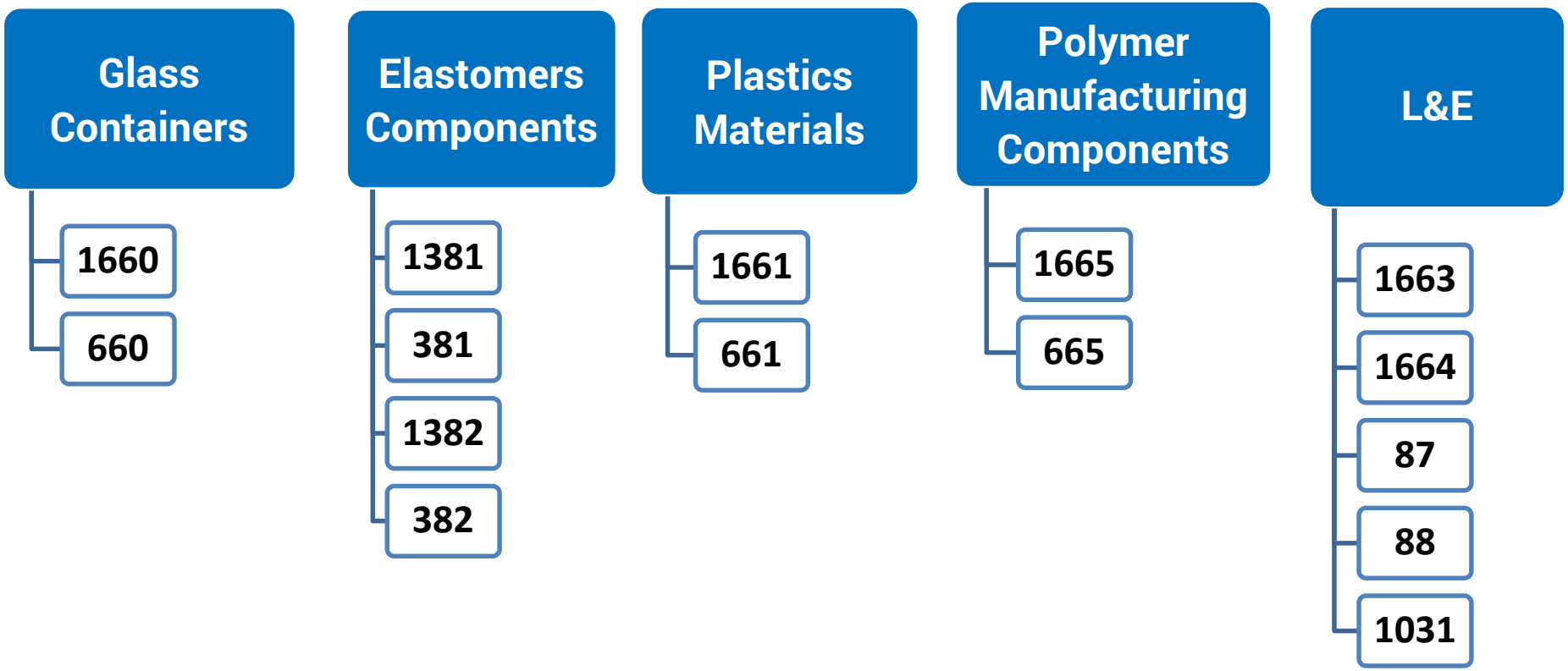
FDA Guidance on Immunogenicity Assessment for Therapeutic Protein Products*

L&E Guidance and Recommendations

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

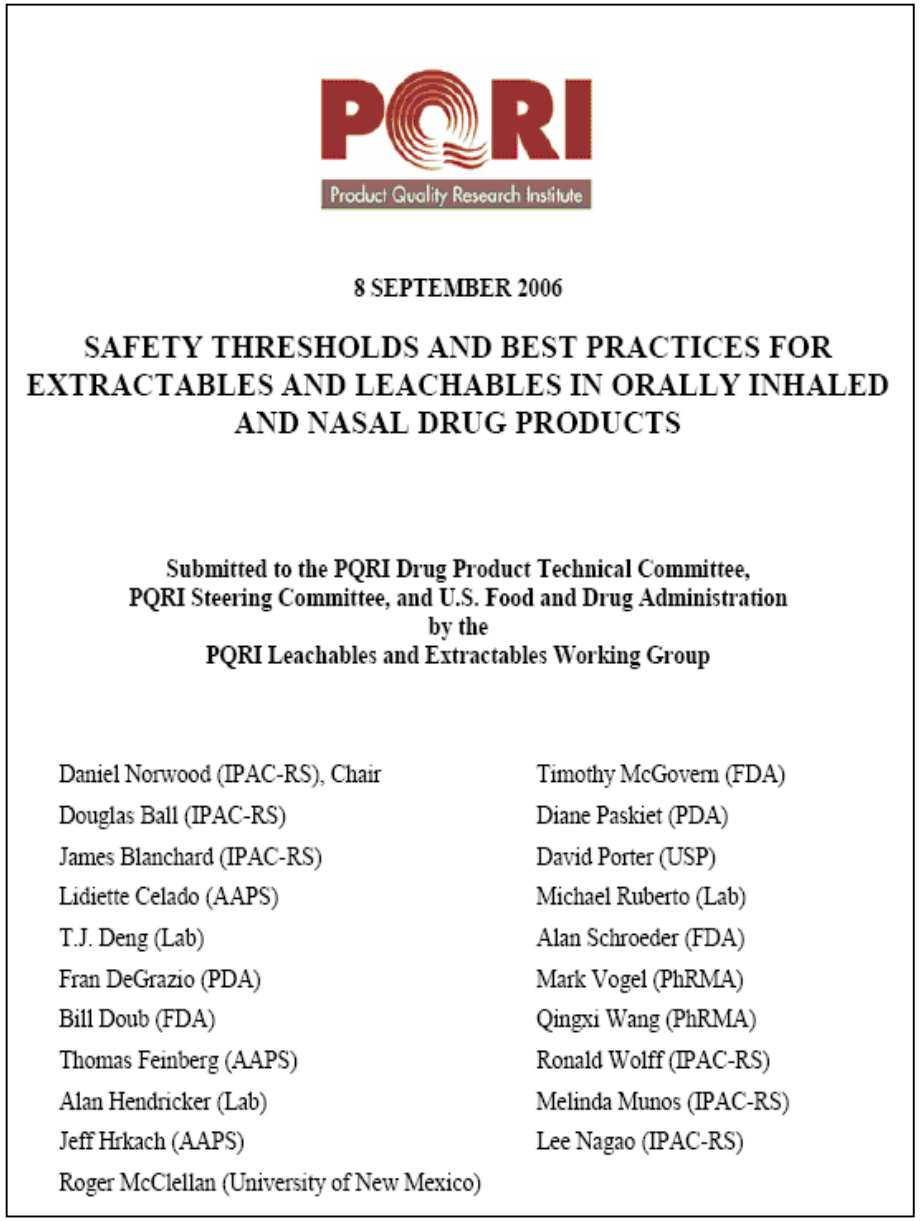
Extractable and Safety Tests Vary by Extraction/Conditions

USP Relevant L&E Chapters



Chapters > 1000 Informational; Chapters< 1000 Specifications
USP Testing is a Starting Point to Qualify for Use

PQRI Finding Leachables: The Forest Through the Trees



PQRI
Product Quality Research Institute

8 SEPTEMBER 2006

SAFETY THRESHOLDS AND BEST PRACTICES FOR EXTRACTABLES AND LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS

Submitted to the PQRI Drug Product Technical Committee,
PQRI Steering Committee, and U.S. Food and Drug Administration
by the
PQRI Leachables and Extractables Working Group

Daniel Norwood (IPAC-RS), Chair
Douglas Ball (IPAC-RS)
James Blanchard (IPAC-RS)
Lidiette Celado (AAPS)
T.J. Deng (Lab)
Fran DeGrazio (PDA)
Bill Doub (FDA)
Thomas Feinberg (AAPS)
Alan Hendricker (Lab)
Jeff Hrkach (AAPS)
Roger McClellan (University of New Mexico)
Timothy McGovern (FDA)
Diane Paskiet (PDA)
David Porter (USP)
Michael Ruberto (Lab)
Alan Schroeder (FDA)
Mark Vogel (PhRMA)
Qingxi Wang (PhRMA)
Ronald Wolff (IPAC-RS)
Melinda Munos (IPAC-RS)
Lee Nagao (IPAC-RS)

- 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 proscriptive***

Application to Parenteral Drug Products to be Released Soon

PQRI Risked-Based Approaches for L&E Testing

Experimental	Key Characteristics
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-sollvents

Detection of:
Organic
Volatile
Semi volatile
Non volatile
Inorganic

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

Proposal	Class I No Genotox	Class II No Genotox	Class III Genotox M7
Threshold (µg/day)	50 If Systemic	5 If Irritant/Sensitizer	1.5 To **Identify**

Best Practices

Characterization	Simulation	Leachables
Material Chemistry	Mimic Actual Use	Actual Drug Product

LVP, SVP, PFS Applications

Considerations Given

Ophthalmics

Biologics

Assessing L&E Risk: PQRI and USP Alignment

Identify Extractable Risk/Uncertainty

$$A \rightleftharpoons B$$

Extent

Patient Contact
Dosage Form
Surface Interfaces

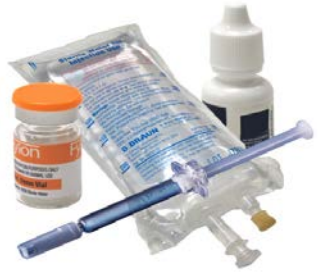
$$r = k[A]^x[B]^y$$

Rate

PQRI

USP

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**

Thank You!

Booth #3

West