PQRI PODP Extractables & Leachables Workshop

Considerations for Biologics Safety and Compatibility of Container Closure Systems

Diane Paskiet, MS, West Pharmaceutical Services

PODP Chair

PQRI

Product Quality Research Institute

April 2018

Part 4: Considerations for Biologics

PQRI Safety Thresholds and Best Demonstrated Practices for Parenteral Drug Products

I. Biologic Products

U.S. Code, 42 U.S. Code § 262

"Biological product is defined, in relevant part, as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings"

Challenges

Biologics are derived from living cells or organisms with a distinctive three dimensional structure, typically of high molecular weight. Due to the origin of biologics and their complex manufacturing processes, a broad range of process- and product-related impurities can exist.

Risk to Biologic Quality

- The molecules are often unstable at room temperature and can be difficult to solubilize and stabilize.
- Attributes critical to biologic quality include:
  - Aggregation
  - Deamidation
  - Oxidation
- Formation of clipped variants, can compromise product stability and safety, including immunogenicity.
- Even well-characterized biological products may pose risk of immunogenicity to varying degrees.

FDA Guidance: Immunogenicity Assessment for Therapeutic Protein Products. 2014

II. Biologic Quality Considerations

The final biologic product quality depends on defining critical product properties and the extent to which they can vary without affecting the safety or efficacy.

- Considers numerous quality attributes and sensitivity to physical and chemical stressors
  - Includes freeze-thaw cycles, agitation, light, pH, and other environmental effects.
- Leachables may compromise patient safety from direct inherent toxicity and/or interaction with the protein indirectly modifying product quality
  - Can originate from the manufacturing process or from container closure and delivery systems.

Biologic Sensitivities

- Physical and chemical stressors
  - freeze-thaw cycles
  - agitation
  - light
  - pH
  - Other environmental effects
- Impurities or contaminants can be of a known structure, partially characterized, or unidentified.
  - Process-related impurities
  - Product-related impurities
    - Arise during manufacture and/or storage

Defining Critical Product Attributes

- Considers a wide array of analytical techniques to determine:
  - Physicochemical properties
  - Biological activity
  - Immunochemical properties (if any)
  - Purity/Impurities/contaminants
- Completely characterize biologic products is difficult
  - finite changes are not easily detected unless they impact the activity and function of the protein during routine testing
- Interactions between therapeutic protein products and the container closure systems may adversely affect product quality, safety and immunogenicity.

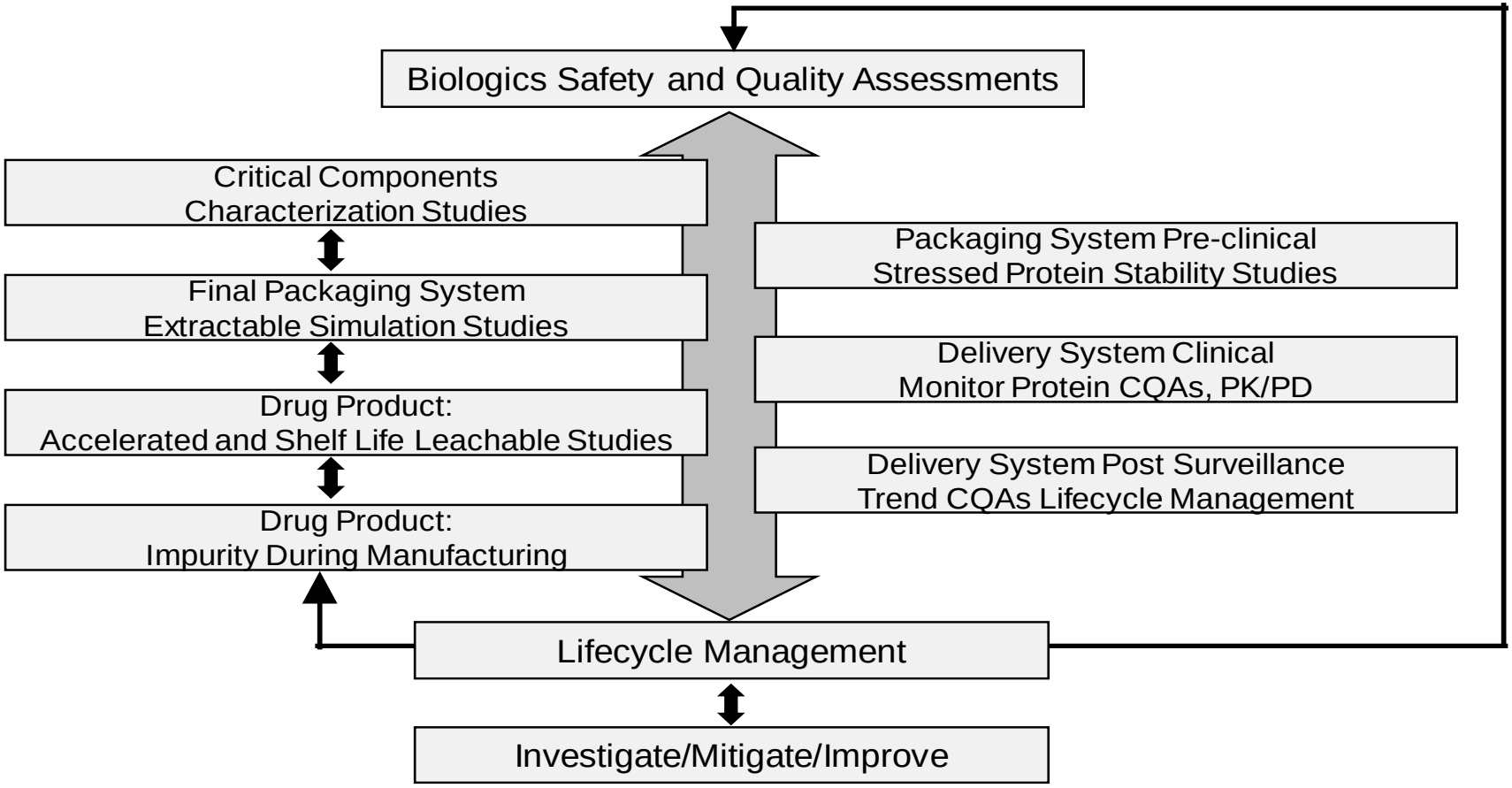
– *FDA Guidance: Immunogenicity Assessment for Therapeutic Protein Products. 2014*

Material Compatibility

Consider Impact of contact materials during development and throughout the product lifecycle.

- The abundance of both hydrophilic and hydrophobic sites and extensive surface area of a protein can serve as potential interaction sites.
- Risks include particulates, aggregation due to environmental changes, contact material surface chemistry, morphology, and system interfaces.
- Interactions between therapeutic protein products and the container closure systems may adversely affect:
  - Quality
  - Safety
  - Immunogenicity

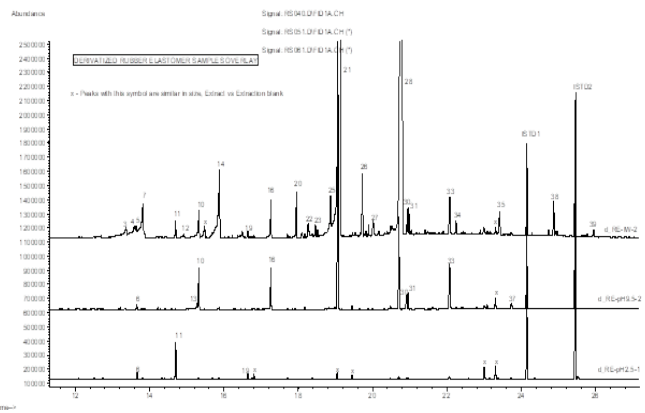
Quality-Compatibility Dynamic Correlations



Container closure/delivery systems attributes; material extractability, physicochemical compatibility, and biologic safety.

Extractables

- Chemical characterization profiles can provide information on what should exist, what could exist, and what could interact with a biologic to impact patient safety. Throughout the biologic lifecycle, there is a wide variety of materials, components, systems, and processes to qualify for intended use
- Not all materials will require the same type of assessments due to their intended applications.

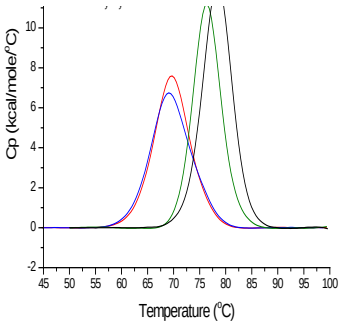


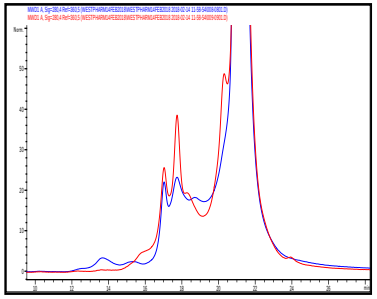
Biologic Quality – System Compatibility Risks

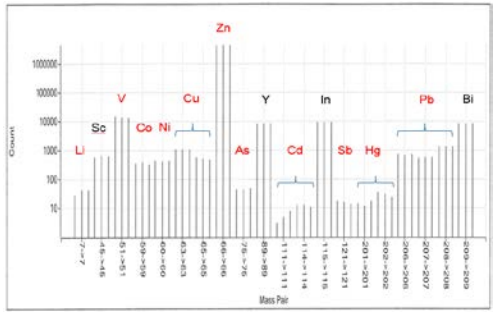
- Material Characteristics
  - Chemical characterization
  - Volatility, absorptivity, permeability polarity, physical properties
- System Characteristics
  - Lubricity, fit, functionality, performance
  - Extractable profile
- Include the potential for
  - Component Crazing- Breakage
- Surface Characteristics
    - chemistry, texture, tension, charge
- System fit- surface interfaces
- Particle generation
    - Inherent, intrinsic , extrinsic

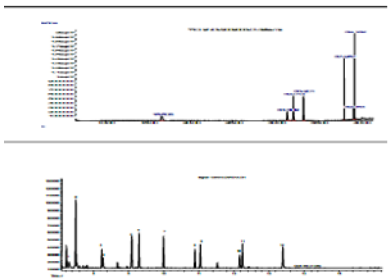
Material Characterization-Biologic Purity/Stabilty

- Chemical characterization study should provide a robust profile of organic and inorganic extractables as a starting point, without compromising the surface integrity of the material.
- The correlation of extractables to leachables with product quality is a dynamic process that involves understanding changes in the product attributes with respect to leachables compatibility, and safety throughout the product lifecycle.



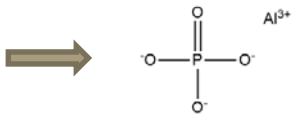




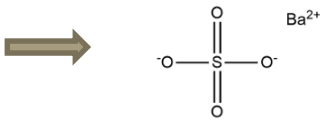


Safety & Quality Examples

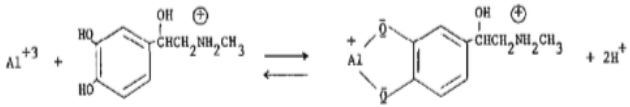
- **Visible particulates**: elements leached from glass
  - Leached aluminum + sodium phosphate buffer



  - 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

$WO_3 \rightarrow Na_2WO_4 \cdot 2H_2O$

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

Immunogenicity

- Particulates are inherent to protein products and critical to the control of biologic quality having potential to cause immunogenicity.
  - Subvisible- submicron

Risk @ -70C for Particles/Lamella, Leachables

Antibody	Lamella	ppb Si	ppb B	ppb Al*
Control	0	11,954	1,085	53
A (-30C)	0	11,589	1,140	43
B (-30C)	0	11,949	1,334	52
C (-70)C	13	11,686	1,123	35
D (-70C)	30	12,124	1,302	31
E (-70C)	17	11,082	939	29
F (-70C)	5	11,531	1,068	31

*Placebo samples and control showed 2-5 ppb leachable Al

Adapted from G. Jiang et.al , Novel Mechanisms of Glass Delamination in Type1A Borosilicate Vials Containing Frozen Protein Formulations PDA J Pharm Sci and Tech 2013

III. Biologic Container Closure

Lifecycle Stage	Upstream	Down Stream	Finish Fill	Clinics
Process Step Unit Operation	Expression Vector Cell line production Cell banking Bioreactor Transfer	Purification process Chromatography Viral Clearance Formulation Filter Storage/Transport	DS Thaw-Pool-Mix Formulate Sterile filter Fill/Finish **Storage** Shipping	Storage Performance Safety Compatibility Protection Functionality
Contact Components	Cell/Bio Container Mixer Bags O-ring Connectors Tubing Bioreactors	Bio/containers Resins Filters/O-rings Tubing/Connectors Needles Sensors DS Containers	**Containers** **Needles/Tubing** **Connectors/O-rings/Filters** **Component Packaging** **Delivery System/Devices** **Secondary Packaging, Labels** **Shipping**	Delivery System Devices Secondary Packaging Labels Ancillary Materials
Contact Solutions	Raw materials Excipients Media	Raw materials Excipients Resin	Raw materials Excipients Resin	**IV diluents** **Water for Injection (WFI)** **Final Formulation**

Risk Based Assessments

- Biologic quality attributes & extraction propensity of the formulation
- Type of materials & components comprising a system and requirements
  - Proximity of the component to the drug product
  - Component performance requirements and intended use
  - In use and storage temperatures
  - Duration of product contact
  - Contact surface area and system interfaces

Identification of risks with scientifically justified studies and clinically relevant data will lead to identification of control points.

IV. Compatibility of Container Closure Systems

- Unique factors to be considered when translating suitability of components/system to biologics molecules.
- A number of functional, physical and chemical compatibility factors should be understood.
- The biologic stability and safety will be influenced by the performance of each component in a container and delivery system.
  - Protect the drug product
  - Compatibility with the packaging system
  - Comprised of safe materials
  - Meet performance and system functional requirements

Suitability Factors

Protection	Compatibility	Safety	Performance
Degradation	Loss of potency	Leachable Induced Toxicity	System Fit
Product loss	Product adsorption	Toxic Impurities	Accurate Dose Delivery
Gas Permeation	Precipitation	Immunogenicity	Shear force Impact
Water Vapor Permeation	pH shift	Altered Conjugated Forms	Freeze-Thaw Cycles
Microbial Contamination	Aggregation	Isomerization	Physical Attributes
Leakage	Impurities	Adduct Formation	Mechanical Attributes
Deep Cold Storage	Surface Interfaces	Structural Stability	Hydrophobic Surfaces
Agitation	Surface Morphology	Unfolding	Sterilization/Aging
Foreign Particles	Reducing Agents	Aggregates	Ease of Use

V. Material Qualification Considerations

- Biologic products pose a unique set of safety risks due to the inherent capacity of a biologic to become unstable, or to adopt multiple conformations or alterations in the primary structure.
- Safety Concern Thresholds for toxic leachables are applicable to biologics, but in addition, **non-toxic** leachables and incompatible contact materials can affect patient safety.
- Considerations for evaluating the **safety of biologic products requires a holistic assessment** of packaging materials that can be correlated to the product's quality attributes and the potential for immunogenicity

Impact of Biologic Formulation

- The biologic formulation is the vehicle to stabilize and deliver the biologic products.
  - Extraction propensity is wide ranging based on formulation ionic strength and polarity
- The design of methods to screen for compounds that pose a risk to protein quality should be based specifically on associated quality attributes
- **Targeted studies based on chemical characterization data should be considered for complex formulations**.

Biologic Formulations

Detecting and identifying leachables) in biologic formulations is a challenge due to several factors, such as masking an unknown chemical entity or interactions influencing quality

Formulation Agents	Impact	Examples of agents
Buffer	Maintain pH, Prevent aggregation and improve conformational and colloidal stability	**Citrate, Histidine, Acetate, Phosphate**
Tonicity	Enhance solubility, conformational and colloidal stability and minimize intermolecular attraction, tonicity, storage	**Sodium Chloride, Potassium Chloride, Mannitol, Sorbitol**
Stabilizer	Minimize aggregation and enhance conformational and colloidal stability, tonicity, reducing viscosity	**Sugar Based Excipients, Sucrose, Trehalose, Glycerol, PEG, Amino Acid Based Excipients**
Surfactants	Minimize aggregation, interfacial stress and improve conformational and colloidal stability	**Polysorbate 20, Polysorbate 80 and Poloxamer 188**
Chelators	Minimize metal impact on biologics	**EDTA, DTBA**

Component Qualification Studies

- Materials will not hasten the deterioration of the product or otherwise render it less suitable for the intended use.
- Final containers and closures will be 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.
- Filling and sealing will be performed in a manner that will maintain the integrity of the product during the dating period.

VI. Injectable Delivery Systems

- Delivery Systems can be subject to different regulatory requirements depending on:
  - intended use
  - technological characteristics
  - proposed labeling
  - packaging
- Interaction between the injector materials of construction, manufacture, and process residuals with the drug/biological product should consider
  - affect the performance of the injector or the product.
- **The testing should include functionality of the entire product-use cycle in the stability program**.

Identification and Mitigation of Risks

- Changes in the dosage form purity, safety, stability
- Changes in the product appearance, physicochemical and molecular structure
- Loss of potency due to absorption or adsorption of the active drug substance
- Degradation of the active drug substance induced by a leachable
- Reduction in the concentration of API or excipient due to absorption or adsorption
- Leachable-induced changes in formulation pH, product degradation, precipitation, aggregation
- Changes in the packaging component or system (discoloration, surface characteristics, component function, brittleness etc.)

Biologic Quality

- The safety and compatibility of packaging materials with biologic molecules are not readily discernable due to the complexity of biologic molecules and the potential for leachables to reversibly or irreversibly interact and affect product quality.
- Cold storage may minimize leachables but not necessarily overcome all compatibility issues.
- Understanding material chemistry, potential leachables and surface interfaces is an important aspect for qualifying material safety and compatibility.

PODP Thresholds

- Initial chemical characterization studies can employ the safety concern threshold (SCT) of 1.5 µg total daily intake (TDI) to derive the analytical evaluation threshold (AET) for the identification of potential toxic compounds in PODP.
  - Extremely trace levels of toxic or nontoxic leachables, foreign contaminants and other impurities can have a significant impact on the product quality attributes.
- Biologic quality can be more sensitive to a nontoxic leachable or to a known hazard at levels well below the SCT.
  - Examples of these could include aldehyde, ketones, free radicals, peroxides, solvents, moisture, oxygen, metals, and silicone.
  - Particular risk to biologic quality is associated with silicone, polytungstate and glass lamella
  - Highly reactive organic and inorganic compounds may pose a risk of irreversible, covalent binding with protein (i.e., adducts, aggregates), which may indirectly compromise product safety and quality

Extractable Risk Assessments

- Extractable compounds that can potentially bind covalently to protein include:
  - Michael acceptors
  - Schiff base formers
  - Acylating agents
  - Aliphatic nucleophilic substitutions
  - Aromatic nucleophilic substitutions
  - Transition metals
- The screening of materials for such highly reactive extractables can help to target these compounds as potential leachables in final drug products.

Summary

- The risk to protein quality can be assessed on the basis of extractable profiles that are derived from chemical **Characterization studies** using exaggerated extractions to provide the basis of material chemistry
- **Simulation studies** can inform the propensity for chemicals to migrate as potential leachable targets.
- Material characterization knowledge, together with biologic characterization data from preclinical and clinical studies, is an important aspect to inform the basis for delivery system safety and compatibility

Biologics Recommendations

- Considerations for comprehensive risk assessments should include biologic activity, efficacy and safety related to the following:
  - Leachable interactions affecting product quality attributes, i.e., degradation, oxidation, chemical modification, immune adjuvant activity
  - Aspects of material compatibility, surface characteristics, organic/inorganic alert compounds
  - Individual components and system interfaces, performance and functionality
  - Leachables assessment performed on the product under stress conditions, and under real-time storage.