PDA Training Course Extractables & Leachables

23-24 October 2025

Biological products – E&L

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Nelson Labs A Sotera Health company

CONNECTING PEOPLE SCIENCE AND REGULATION®

Setting the stage

1. What are biological products?
2. What sets biological products apart from small molecule drug products and why it matters?
3. Where do we stand / what is current knowledge?
4. What are specific E&L consideration?

Biological products

Biological products

virus

toxin

antitoxin

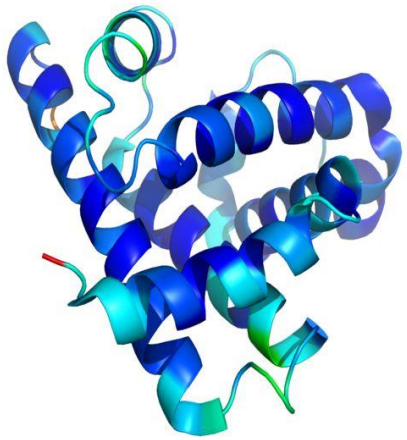
therapeutic serum

blood component/derivative

blood

protein

allergenic product



Applicable to the prevention, treatment or cure of a disease or condition of Human Beings.

What sets biological products apart and why it matters?

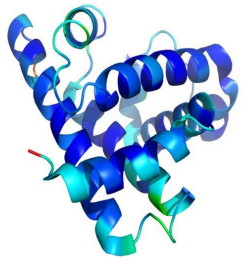
What sets biological products apart and why it matters?

Biologics require special care:

- Administration by injection is among those of highest concern

- Likelihood of interaction between packaging component and injectable dosage is high

- **Biologics are complex**
  - ✓ Large molecular weights
  - ✓ Many binding sites on the surface (hydrophilic and hydrophobic)
  - ✓ Heterogeneous mixtures



Biologics require special care:

- Biologics are sensitive to structural modifications
  - ✓ Safety considerations (**immunogenicity**)
  - ✓ Efficacy considerations (loss of activity, formation of neutralizing antibodies)
  - ✓ Quality considerations (protein aggregates, stability)

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Consequences of IMMUNE RESPONSES

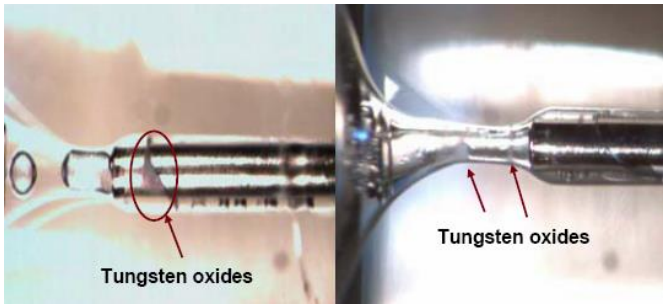
From *"no apparent effect"* to *"serious adverse effects"* that could be **life threatening**

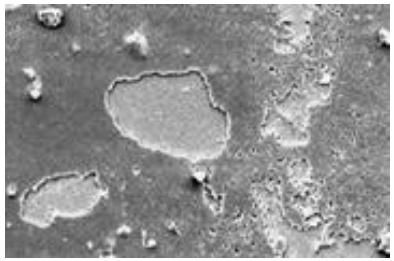
immunogenicity

May be caused by **interactions between the Protein and Packaging**

What sets biological products apart and why it matters?

- Organic Compound with Immunomodulatory activity
- Polysorbate containing formulations (Erythropoietin - EPO)
- Oxidized metals causing Aggregates
- Silicone lubricants
- Polytungstate
- Glass Lamellae
- **Reactive compounds** may cause COVALENT irreversible bonds



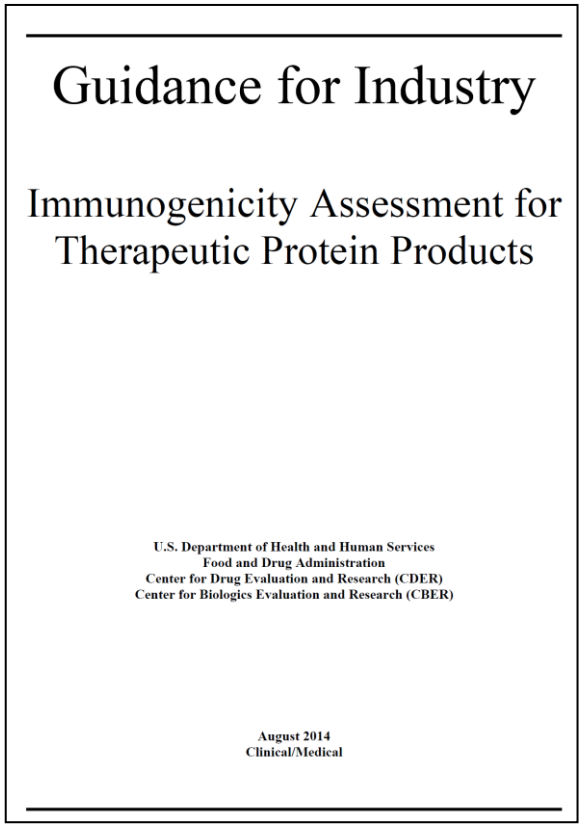


glass delamination

Where do we stand?

Where do we stand?

2014


Guidance for Industry

Immunogenicity Assessment for Therapeutic Protein Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2014
Clinical/Medical

Sponsors should conduct a comprehensive E&L assessment to assess the attributes of packaging that could interact and degrade protein therapeutic products and possibly alter product quality and immunogenicity

Where do we stand?

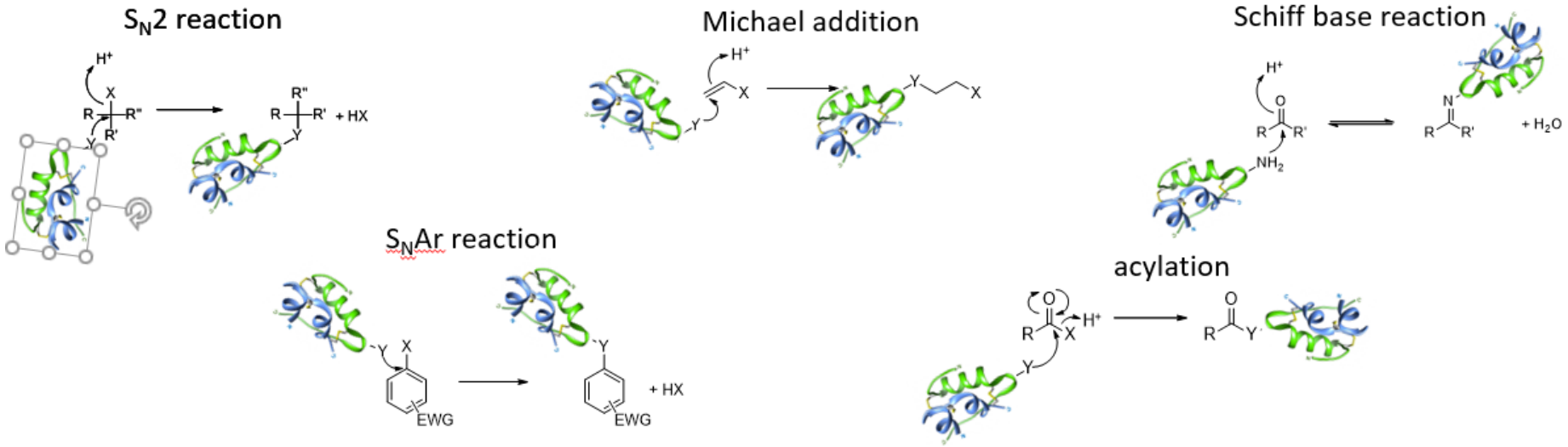
2015

PDA Journal
of Pharmaceutical Science and Technology

Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products

Kim Li, Gary Rogers, Yasser Nashed-Samuel, et al.

PDA J Pharm Sci and Tech 2015, *69* 590-619
Access the most recent version at doi:10.5731/pdajpst.2015.01073



Where do we stand?

2022

PQRI
Product Quality Research Institute

Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)

Where do we stand? PQRI

- QUALITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS
- MANUFACTURING / PACKAGING COMPONENTS IN CONTACT WITH BIOLOGICAL PRODUCT
- SUITABILITY OF PACKAGING AND DELIVERY SYSTEMS
- CONSIDERATIONS FOR QUALIFICATION OF CCS AND DELIVERY SYSTEM COMPONENTS

Where do we stand? PQRI

- QUALITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

Final Biological Product QUALITY depends on:

- Defined Critical Quality Attributes (CQA's)
- Extent to which they can vary WITHOUT affecting the Quality and Safety

Critical Quality Attributes (CQA) could be e.g.:

- Freeze-thaw cycles
- Agitation
- Light
- Environmental effects

Where do we stand? PQRI

- QUALITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

IMPURITIES can be

- Known
- Partially characterized
- Unidentified

PROCESS RELATED IMPURITIES

- From starting materials
- Equipment and Manufacturing
- Downstream processing

PRODUCT RELATED IMPURITIES

- Arise during Manufacturing and Storage
- No Comparable properties of the desired product for activity, efficacy, or safety.

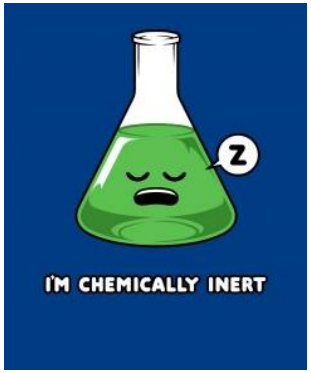
Where do we stand? PQRI

- QUALITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

If PROCESS/PRODUCT related impurities are known to be introduced

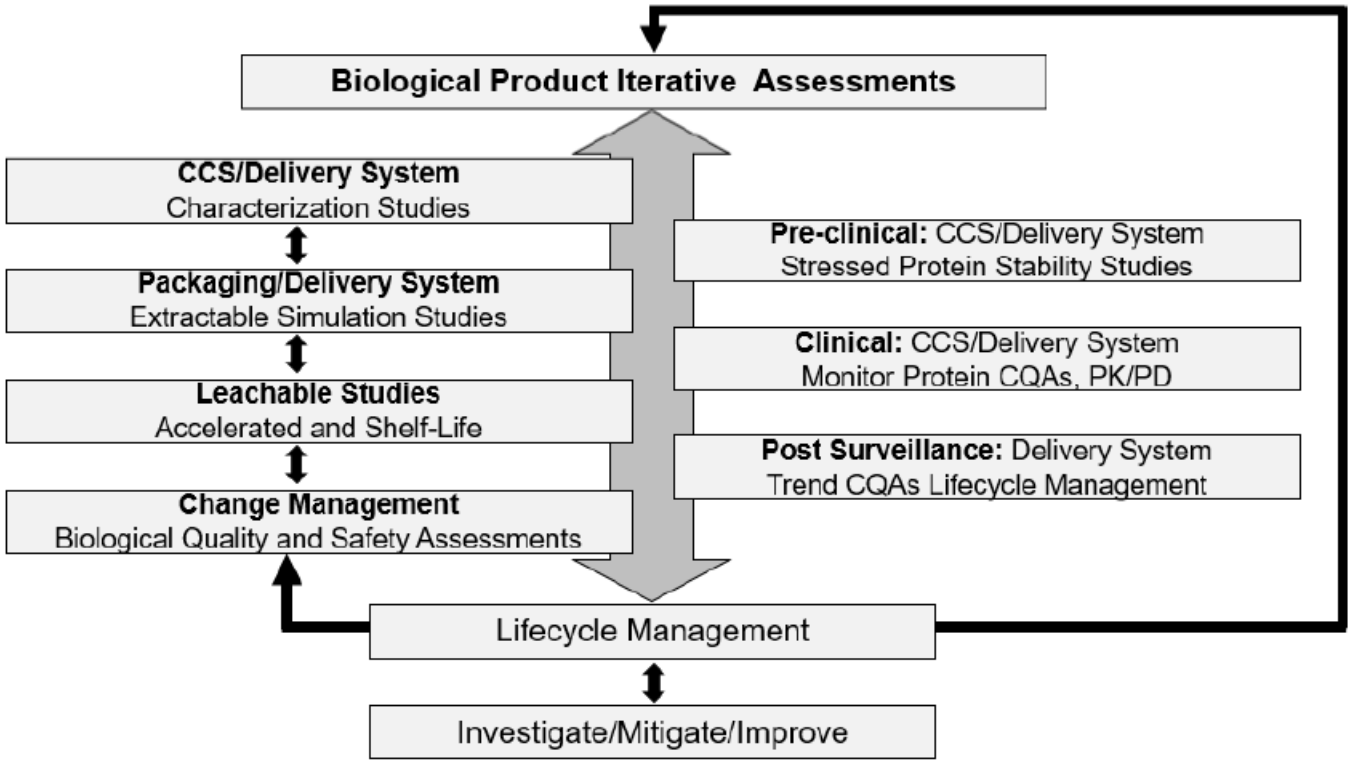
- Determine levels
- Define acceptance criteria

Container/Closure system and components need to be proven chemically inert



Where do we stand? PQRI

- QUALITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

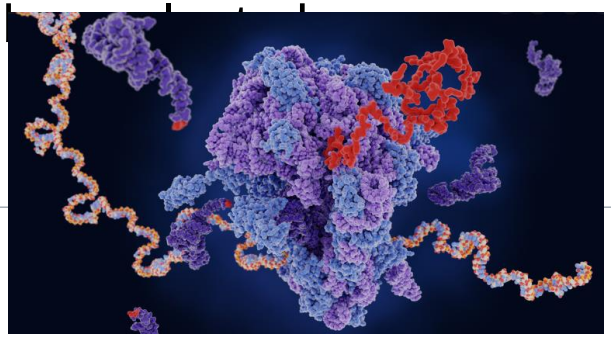


Where do we stand? PQRI

- QUALITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

COMPREHENSIVE CHARACTERIZATION OF THE BIOLOGICAL PRODUCT

- Is KEY to understanding the potential risks related to manufacturing an CCS
- Compatibility of Final Device is VITAL to ensure
  - Stability
  - Effectiveness
- The CCS will be qualified in the context of the biological product
- Changes in Formulation, Manufacturing and Components should be assessed during the LIFE CYCLE of the product and the risk to Quality and Safety should b



Where do we stand? PQRI

MANUFACTURING / PACKAGING COMPONENTS IN CONTACT WITH BIOLOGICAL PRODUCT

Components: the physical and mechanical performance relate to chemical make-up

- Sources of potential Leachables
  - Chemical composition of the material
  - Effects from processing (mold release, lubrication, adhesives…)
  - Post processing (eg sterilization, cleaning, storage…)
  - Assembly of the systems

- Important to ANTICIPATE chemical entities that could
  - Leach into the Biological Product
  - Could INTERACT with the Biological Product
  - Could impact both the Quality and Safety of the Drug Product

MANUFACTURING / PACKAGING COMPONENTS IN CONTACT WITH BIOLOGICAL PRODUCT

Occurrence of Leachables: influenced by Extraction Propensity of the Biological Product

Primary: DIRECT contact with the Biological Product

Secondary & Tertiary: INDIRECT contact with the Biological product

- Labels, Ink, Carton, adhesives, inserts, overwraps

Probability of higher concentration of Leachables originating from Primary Packaging is HIGHER than Leachables originating from Manufacturing Systems

- Primary Packaging: longer contact
- Manufacturing Equipment: shorter, transient contact, potential removal (filtration) steps

MANUFACTURING / PACKAGING COMPONENTS IN CONTACT WITH BIOLOGICAL PRODUCT

Materials of Construct, Surface finishes and Processing Aids affect Suitability

Risks for Leachables should be considered in

- Pre-Formulation
- Final Formulation
- Clinical Use,
- Commercial use

Perform **RISK EVALUATION** for Potential Interaction of Biological product with components

- Knowledge of the components
- Intended system and application
- Clinical: Primary packaging first
- Evaluate potential risk of EXTRACTABLE compounds with the Biological Product
- Cold Storage
  - May minimize Leachables, HOWEVER, it does not overcome all concerns

SUITABILITY OF PACKAGING AND DELIVERY SYSTEMS

Relies on the raw materials of the components of raw materials.

The Materials Chemistry is FUNDAMENTAL to

- Physical properties
- Functional Properties
- Protection of the Biological Product
- Safe and effective dosing, which requires
  - *Dimensional stability of the components*
  - *Proper Fit of the multiple parts*
  - *Seal integrity*
  - *Performance of the final system*

SUITABILITY OF PACKAGING AND DELIVERY SYSTEMS

Risk to performance of the CCS should include:

- Gas permeation
- Failure /Breakage
- Surface Interaction *(adsorption, absorption, protein degradation, (sub-)visible particle formation…)*
- Material Swell
- Outgassing

- Extractable profile should provide information on “potential” leachables

- CCS Risk assessments should include comprehensive understanding of materials CHEMISTRY

SUITABILITY OF PACKAGING AND DELIVERY SYSTEMS

SUITABILITY OF CCS

- Materials that are suitable for EVERY application are not Practical
  - A broad diversity of performance requirements

- **Consider a "HOLISTIC" Approach!**

The Biological Product STABILITY & SAFETY will be influenced by performance of each component

Specific E&L considerations?

Specific E&L considerations

- SCT/AET: Applicable to the Biological Product, indicating potential Toxic Leachables
- HOWEVER: non-toxic leachables & material incompatibility could also affect patient safety
- Design Studies in a way to identify risks for
  - Potential leachables
  - System incompatibilities
- That could destabilize or interact with the final drug product
- Stability Studies
  - Under Stress/Accelerated conditions
  - Take into consideration potential leachables that could interact or degrade therapeutic protein

Specific E&L considerations

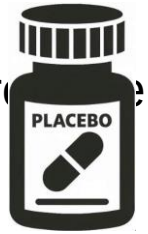
Detection and Identification of Leachables can be difficult in Biological Product!

- Often complex formulations
- Can obscure known/unknown chemical entities, labile compounds
- Formulation may degrade (e.g. auto-oxidize)
- May interact with excipients, or with other leachables
- Surfactants: greater potential for leachables from non-coated rubbers
- EDTA containing formulations: facilitation of metal ion migration
    - can covalently bind and oxidize Biological Product

Specific E&L considerations

Leachable Study Design should combine a Targeted and Non-Targeted Approach!

- **Targeted:**
  - Based On the information from a comprehensive Extractable Study
    - Organic Extractables
    - Inorganic Extractables



  - Simulation Studies to facilitate the Identification and Quantification of pr[illegible]e Leachables to be tox assessed
    - Should identify “Compounds of Concern”

  - Develop, Optimize and Validate Targeted Analyte Methods

Specific E&L considerations

Leachable Study Design should combine a Targeted and Non-Targeted Approach!

- **Non-Targeted:**
  - Useful in the detection of unanticipated leachable compounds
  - Not optimized (eg in sensitivity or specificity)
  - Screening for
    - Highly reactive Compounds
    - Compounds with a high toxicity risk
    - Compounds that could affect the Quality attributes of the Biological product
  - However, try to include as many critical compounds in Targeted analysis
- **Make a Correlation of Extractables to Leachables, and assess impact on Quality:**
  - Important to understand changes in product attributes

Key take-aways

Key take - aways

- **Gather** as much knowledge and **information** as possible on the **materials of constructions of the Components**

- Perform a **Comprehensive Extractable Study** to establish a detailed Extractable Profile under relevant but worst case conditions
  - *Organic Compounds*
  - *Inorganic Compounds*

- **Evaluate the Extracted Compounds** on their
  - *Toxicity*
  - *Potential Reactivity with the Biological Product*

- Perform **Spiking Studies** to understand the impact of “red Flag” Compounds on the safety and quality of the Biological product
  - *Evaluate the impact on CQA’s for Biological Product*

Key take - aways

- **Design the Leachable study** on the outcome of a comprehensive Extractable study with a subsequent in-depth evaluation (toxicity, potential reactivity of extractable compounds)

- Use the **"General" SCT/AET considerations** (SCT of 1.5 µg/Day for Chronic, 5µg/day for non-chronic treatments)

- HOWEVER: both Toxic and Non-toxic **compounds may be detrimental to the Quality** of the Biological Products **at levels lower than the AET**

- Use **Targeted Methods** that are developed and validated for specific target compounds. The selection of these compounds should be based on
  - *Their toxicity*
  - *Their potential Reactivity (results of "spiking" experiments?)*
  - *Look for secondary leachables (formed after a reaction between a reactive leachable and ingredients of the biological product)*

Key take - aways

- Combine Targeted Methods with **Non-Targeted methods**, enabling the detection of
  - *Unexpected Leachables*
  - *Reacted Leachables*
- **Identify and Quantify** all leachable **compounds above the respective AET** level
- Perform a **Correlation** between the **Extractables** data and the **Leachables** found
  - *Identity*
  - *Quantity*
- Perform a **Safety Evaluation** on the detected and reported Leachables