Nelson Labs®
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# In-House Training Course

# EXTRACTABLES & LEACHABLES

*Developing Extractable & Leachable Qualification Strategies for Pharmaceutical Container/Closure systems & Single-Use Systems in Bioproduction*

When making drug products, pharmaceutical companies are faced with the need to further investigate the materials that will be in contact with the drug product in its final packaging during manufacturing, intermediate storage, final storage, or during the delivery of the drug to the patient. While historically the potential safety issues were the main driver in these kinds of investigations, recently quality issues – i.e. for biopharmaceuticals – have become an additional concern.

## This training course will look at Extractables & Leachables from many different angles:

Definitions, Regulatory, Material & Polymer Science, Analytical E&L Methodologies, Safety Assessments, and Study Design for a different and wide variety of pharmaceutical primary packaging systems.

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## WHO SHOULD ATTEND?

- Pharmaceutical Packaging and Device Engineers
- Production Engineers, using SU systems
- Regulatory Affairs Officers
- Pharmaceutical R & D Managers
- Analytical Chemists, working on E&L
- Quality Assurance Officers
- Toxicologists and Safety Assessors

## LEARNING OBJECTIVES

Upon completion of this workshop, you will be able to:

- Explain in detail the current regulatory requirements for container/closure (C/C) qualification from an E&L perspective
- Explain the upcoming changes in regulations, standards, and recommendations from PQRI, USP and BPOG and how these changes could impact a future evaluation of a pharmaceutical C/C-system
- Understand the materials of construction – and their composition – of container closure systems, and how they could impact the safety and quality of a parenteral drug product
- Put together an evaluation program (review of provided documentation, analytical testing) of different types of parenteral drug product container/closure systems
- Perform a safety/risk assessment of analytical results, obtained after completion of an E&L study

## COURSE FORMAT

The course can be given in a wide variety of formats and can be tailored to the needs of the client. This means that the training can be organized either face to face on your site, or created as a virtual learning experience. The number of participants will depend on the design of the learning process. The class can be organized physically on site or be available virtually (online) for all employees of your different subsidiaries. Nelson Labs will be very flexible in the design and execution of this educational experience for your organization.

**For more information regarding this training**
and how we can create the best learning experience for your employees,
contact us at **infoeurope**@**nelsonlabs**.com.

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## A helicopter view of the potential learning modules within the scope of the program

### Intro to Extractables & Leachables

- What is the importance of a good E&L qualification?
- Understanding the definition of Extractables and Leachables
- Defining the different steps in the E&L process and how they interact with each other
- Historical cases of leachables impacting the quality or the safety of a drug product
- High-level view of the global regulatory requirements (FDA, EMA, etc.) for primary packaging

### Understanding Polymers Used in Manufacture of Pharmaceutical Containers & Closures

- Classification of polymers: types of polymerization, physical properties, and consequences for E&L considerations
- Understanding the composition of polymers
- Making the distinction between compounds that are intentionally added to a material/polymer and substances added unintentionally
- Overview of the most common polymer additives: their use and function and how they may potentially degrade
- Oligomers: A very important class of polymer impurities: An overview

### The Mechanism of Leaching

- What are the physicochemical parameters to be considered when trying to understand polymer migration?
- How do leachables move through a polymer? The diffusion model
- Special cases in migration: Outgassing (e.g. lyo applications), supersaturation, and blooming

### High-Level View of Recent & Upcoming Changes to US Pharmacopoeia (USP)

- USP <661> Plastic Packaging Systems and their Materials of Construction
- USP <661.1> Materials of Construction
- USP <661.2> Plastic Packaging Systems for Pharmaceutical Use
- USP <665> Polymeric Materials in Manufacturing of (Bio)Pharmaceutical Drug Products
- USP <1661> Evaluation of Plastic Packaging
- USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- USP <1664> Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery Systems

### How to Perform a Safety Evaluation: Toxicological Risk Assessment of Extractables & Leachables

- Toxicology 101: An introduction to safety assessments of Extractables and Leachables
- Defining the "Big 5": What are the most important toxicological end points that are considered in an E&L safety assessment?
- Other guidelines that can be relevant in a toxicological assessment
  - ICH M7 (DNA reactive Impurities) and it's suggested staged approach (Habers rule)
  - ICH Q3C: Residual solvents
- The Safety Concern Threshold (SCT) and the Analytical Evaluation Threshold (AET) concept of PQRI (OINDP and PDP/ODP)
- Examples

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### How to Set-up Extractable Studies

- Designing extraction studies that are compliant with USP <1663>
- Selecting the right conditions for extraction
  - How to select the right solvent in an extraction study to support the leachable evaluation
  - Considerations of time and temperature of extraction
  - Extraction techniques
- How to include the Safety Concern Threshold (SCT) and Analytical Evaluation Threshold (AET) concepts into the design of an E&L study
- How to select the right compounds to monitor during a leachable study

### How to Set-up Leachable Studies

- Designing a leachable study compliant with USP <1664>
- How to consider the right "blank" solution as a baseline in a differential leachable assessment
- Defining the options for developing quantitative methods in the leachable assessment: From limit test to fully developed and validated methods
- What to do if major analytical challenges would occur in the leachable analysis of complex drug products

### Analytical Techniques to Perform Extractables & Leachables Research

- The importance of sample preparation: The corner stone in E&L research
- What are the target compounds for material research?
- How does classification of these compounds assist in finding the right analytical technique?
- From basic "screening" methodologies to state-of-the-art equipment

### Chromatographic Screening Methodology & Potential Errors to Avoid When Performing Screening

- Defining the Errors possible in chromatographic screening to detect, identify, and quantify organic extractable compounds
- The error of omission: A fatal error
- The error of misidentification: A fatal error
- The error of inaccurate quantification: A critical error
- How to address all these errors

### E&L Testing for Small Volume Parenteral Applications (Liquid Applications)

- Glass vials and syringes: Issues with glass metals leaching, tungsten, glue residues, and silicone oil
- The issue with rubbers: The stopper, the plunger, the needle shield, or the tip cap. Are different approaches needed?
- The special case of rubber oligomers as potential leachables
- Alternatives to glass: COC, COP, and PP
- The impact of secondary packaging: Option or necessity?
- Setting up extractable and leachable studies for a vial containment system (vial and stopper)

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### E&L Testing for Lyophilized Drug Products (Liquid & LYO Applications)

- Containers for lyophilized drug product and the containers for reconstitution solution and administration sets: All have different requirements?
- The problems with finding a right baseline blank solution for the differential analysis of leachables
- Reactive leachables: An often-recurring problem with lyophilized drug product
- The impact of the quality of the rubber stopper on the leachables profile

### E&L Testing for a Large Volume Parenteral Applications

- Helicopter view of the LVP applications
- The specific challenge in E&L testing for LVP's compared to other dosage forms
- Primary packaging for LVPs: Critical materials and components
- The consequence of low AET levels for LVP
  - Analytical challenges
  - Toxicological Evaluations
  - Identification requirements
- Considerations for simulation studies for LVP packaging when one system is used for multiple applications

### E&L Testing for Ophthalmic Applications

- Regulatory requirements for Ophthalmic applications in the US and EU
- Describing the different parts and options for a container/closure system for ophthalmic applications
- The impact of secondary packaging and label migration on the leachables profile: Option or necessity?
- Setting up leachable studies for ophthalmic drug products
- Case studies discussing the typical outcome of a leachable study for ophthalmic drug products, using previously discussed considerations

### E&L Testing for Inhalation Applications

- The diversity of container/closure system types within the OINDP space
- Very high-risk products: The Metered Dose Inhalers (MDIs)
- Dry Powder Inhalers (DPI's): How deep to go in an E&L assessment and what is the risk?
- Nasal Sprays: What are the challenges in establishing an E&L program?

### E&L Testing for Blow-Fill-Seal Applications

- The Blow-Fill Seal Process and the associated choice of materials for the BFS containers
- Typical Applications of blow-fill-seal applications and their consequences or E&L process that needs to be followed
- E&L considerations of BFS applications: Not all about the primary packaging
- Obstacles with the selection of secondary packaging

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### E&L Testing for Dermal & Transdermal Applications

- The observed changes to regulatory requirements for E&L regarding dermal and transdermal products
- Leachable studies for dermal applications: How to frighten an analytical chemist
- Simulation studies valuable in bridging extractables studies and leachables studies: Scientific value of a simulation study versus its regulatory acceptance
- What about transdermal patches?

### The Reactivity of Leachables with Therapeutic Proteins

- The EPREX Case explained from an immunogenicity perspective: Could reactive leachables have played a role?
- Immunogenicity: A high concern for Therapeutic proteins (a regulatory perspective)
- Can the reactivity of leachables be predicted? Developing a reactivity model
- Verifying the reactivity model from an analytical perspective: Can the predicted reactivity be observed in real-life samples?
- Using Insulin (as a peptide) as a marker compound for reactivity with proteins
- Conclusions

### Chemical Characterization According to New ISO 10993-18:2020 Standards

- Chemical Characterization within a risk management perspective described in ISO 10993-1
- Considerations of patient exposure in the development of a Chemical Characterization program
- Selection of solvents, analytical techniques, and associated test article preparation steps
- Determination of exhaustiveness: A key consideration for long-term or invasive contact devices
- AET as a cornerstone of the Chemical Characterization evaluation process
- Which outcomes of a Chemical Characterization study would warrant further follow up in a leachable study?
- How to develop a leachable program for medical devices
- Case studies.

### E&L Testing for Disposable & Single-Use Systems in Bioproduction

- How to classify the risk of different single-use systems in the bioproduction process
- Understanding BPSA and BPOG recommendations: How can they be implemented in the study design?
- Performing E&L studies on filters: Potential approaches

### Case Study Section

- Case study examples for primary packaging: Vial containment system, pre-filed syringes, lyophilized drug product containers, blow-fill-seal applications, large volume parenterals, etc.
- Case study examples regarding the impact of secondary packaging: labels, printing inks, carton boxes, etc.
- Case study examples of single-use systems: bags, filters, tubing

## For more information regarding this training

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**Safeguarding Global Health®**
- with every test we complete.

Nelson Labs is a global leader in microbiological and analytical chemistry testing and advisory services for the medical device and pharmaceutical industries. Nelson Labs serves over 3,800 customers across 14 facilities in the United States, Mexico, Asia and Europe. We have a comprehensive array of over 800 laboratory tests supporting our customers from initial product development and sterilization validation, through regulatory approval and ongoing product testing for sterility, safety and quality assurance.

We are regarded as a best-in-class partner with a strong track record of collaborating with customers to solve complex issues.

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Sterigenics is a leading global provider of outsourced terminal sterilization and irradiation services for the medical device, pharmaceutical, food safety and advanced applications markets. With our industry recognized scientific and technological expertise we help to ensure the safety of millions of patients and healthcare practitioners around the world every year.

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