Extractables & Leachables Summit 2022
Ensuring Quality, Safety, Suitability and Regulatory Compliance for Drugs, Biologics and Medical Devices
September 20–21, 2022, Philadelphia PA

Featuring Lessons Learned and Case Studies from Industry Experts:

- Christopher Houston
  Bausch + Lomb

- Ping Wang
  Johnson & Johnson

- Dujuan Lu
  SGS

- Dennis Jenke
  Triad Scientific

- Sherry Parker
  Wuxi AppTec

- Ron Brown
  FDA (retired)

- Diane Paskiet
  West

- Praneeth Edirisinghe
  Pfizer

- Ted Heise
  MED Institute

- Prabhakar Reddy
  USP

- Mike Ruberto
  Material Needs

- Mike Eakins
  Eakins & Assoc.

- Mark Jordi
  Jordi Labs

- Piet Christiaens
  Nelson Labs

- Eric Hill
  Boston Analytical

- Steve Zdravkovic
  Baxter

- Atish Sen
  AstraZeneca

- Cherry Shih
  Pall

- Gyuri Vas
  Intertek

- Sam Albeke
  VR Analytical

With Comprehensive Coverage On:

- Designing and Improving Risk-Based Assessment of E&L Data for Drugs, Biologics, and Medical Devices
- Novel Approach to Justify Model Solvents and New Screening Tools for Extractables
- ISO 10993-17: Application of Proposed New Approaches to Facilitate Toxicological Risk Assessment of Medical Devices
- Medical Device E&L: The ISO 10993-12 Extraction Conditions Round Robin Study and Its Aftermath
- PQRI Safety Thresholds: Putting in Place E&L Best Practices for Parenteral Drug Products
- Analytical Considerations in Extractables and Leachables Testing of Drug-Device Combination Products
- AETs and Response Factor Variation for E/L Studies
- Impact of Sterilization Methods to Extractable Profiles of Single Use Systems
- Overcoming Common Analytical Challenges in E&L Studies
- Toxicology Assessment for E&L Studies
- Extractables and Leachables Assessments for Lower Risk Dosage Forms
- Chemical Characterization in Biocompatibility for Med Devices
- Extractables & Leachables Case Study for Cream/Gel Drug Topical Drug Product
- E&L Considerations in the Qualification and Validation of Single-Use Systems
- Addressing E&Ls from Bioprocessing Equipment & Product Packaging Perspectives
- And More!

With Representation From:

Contact: Kim Hubbard
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ONdrugDELIVERY
The landscape for E&L assessment has changed over the past two decades. We now have a better understanding of E&L and improved procedures for analyses. Currently updates to regulations and standards are ongoing that will influence E&L assessment in the future. The adoption of ICH Q3E will harmonize the various recommendations, sometimes at odds, that exist currently. Re-defining basic terms such as SCT, AET, UF, etc. will be implemented. Concepts such as migration modelling will be more common. All these changes that will affect E&L will be discussed.

Spotlight on Solvent Selection

The purpose of an extractables study is to identify potential leachables from a pharmaceutical packaging system. The extractables profile of a packaging system depends on the materials used to construct the packaging system and on the chemical and physical properties of the drug product formulation. This presentation introduces the concept of using the dielectric constant to identify an organic solvent system relevant to the drug product formulation. The use of a dielectrically equivalent simple model solvent system to the drug product of interest should generate an extractables profile that is relevant to the drug product formulation. The advantages of this method versus that of the more traditional approach, where exposing the packaging system or its materials of construction to organic extraction solvents designed to generate a worst-case extractables profile, will be discussed. Traditional approaches to generating extractable profiles do not always generate a profile that is relevant to the drug product formulation. This can create a significant burden to not only identify potentially irrelevant extractable compounds, but also significantly increases the scope of toxicological assessments. Furthermore, the exaggerated extractables profile may lead to inappropriate targets being identified for leachables analysis potentially leading to some unexpected impurities in the drug product. The results of a proof-of-concept study performed to demonstrate the relationship between the dielectric constant and the concentration of compounds extracted using various organic solvents will be presented.

The Future of E&L Assessment

Atish Sen, Staff Scientist, AstraZeneca

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Spotlight on E&L for Container Closure Systems & Components for Lyophilized Drug Products

Impact of Sterilization Methods to Extractable Profiles of Single Use Systems

Ping Wang, Director, Johnson & Johnson

The rapid development of biological drug products, such as monoclonal antibodies, vaccines, and cell & gene therapy (CGT) products created great demand for single-use technologies (SUT) in the biomanufacturing process. The sterility of those SUT materials is critically important to product quality and patient safety. The commonly used methods to sterilize the SUT materials include e-beam, gamma irradiation, autoclave, ethylene oxide, and X-ray. Due to the nature of various technologies, the impact to extractable profiles of SUT materials is of concern to drug manufacturers and health authorities. This presentation will compare the extractable profiles of various materials sterilized with different methods (especially autoclave and gamma irradiation). The results could be used to perform risk-based assessment, and evaluate the suitability of extractable data generated with different sterilization methods.

The Necessity of Extractable & Leachable Qualifications for Lyophilized Drug Products: Some Misconceptions Addressed

Dr. Piet Christiaens, Scientific Director, Nelson Labs Europe

When selecting and qualifying the Primary Packaging for lyophilized drug products, one of the obvious questions is, how deep should one go into the E/L-qualification process of a lyo-container? As the drug product is in a solid state, it is expected that the interaction between the lyophilized drug product and the components of a lyo-container will be low. This is also reflected in the USP<1664> Monograph on Leachables and the EMA Guideline on “Plastic Immediate Packaging Materials” (2005). However, the mechanism of interaction between the lyo-cake and e.g., the rubber stopper (when consid-
uring a lyo vial) are not always fully understood. The inter-
action mechanism is based upon "outgassing" of the
rubber stopper, where the lyo cake acts as an adsorbent.
Not only can this lead to substantial accumulation of the
volatile and semi-volatile leachable compounds onto the
lyophilized drug product, it may also induce chemical
reactions between the leachables and the drug product,
i.e., when the adsorbed leachables show electrophilic
properties.

11:55 Complimentary Lunch

1:05 Post-lunch presentation, sponsored by
eurofins EAG Laboratories

Abstract Coming Soon.

1:25 Comparison of the Levels of Rubber Stopper-Related Organic Leachables in Commercially Available Vialled Liquid and Lyophilized Drug Products

Steve Zdravkovic, Research Scientist II, Baxter International

Rubber stoppers that seal the primary packaging sys-
tems of parenteral pharmaceutical products have the
potential to introduce impurities into the drug during
storage. While this interaction has been well character-
ized for products stored as an aqueous liquid, it is not
well understood how the interaction is affected when the
product is stored as a lyophilized solid. Accordingly, the
goal of the study described in this presentation was to
determine how lyophilization affects the propensity for
impurity migration (leaching) into the product. This was
achieved by measuring the concentration of substances
in the stopper and the concentration of these substanc-
es that had leached into the product at equilibrium for
twelve lyophilized and twelve liquid commercial drug
products. These concentrations were then used to calcu-
late equilibrium constants, which quantified the degree
of partitioning of each compound between each unique
stopper and drug matrix, and compare the leaching be-
behavior of each liquid and lyophilized drug product includ-
ed in this study.

Critical Issues—Response Factor Variation in AETs

Mitigating Response Factor Variation in Application of the Analytical Evaluation Threshold, Large UF or Multiple Detectors

Dr. Mark Jordi, President, Jordi Labs

The characterization of extractables and leachables
(E&L) is an integral part of ensuring biocompatibility
for many medical devices and pharmaceutical prod-
ucts. Guidance for E&L has been provided in USP
<1663> and <1664> for pharmaceutical products and in
ISO 10993-18 for medical devices. The first step in the E&L
process involves detection of those compounds which
are suspected to be at or above the level of toxicologi-
cal concern. This process is accomplished through the
use of the Analytical Evaluation Threshold (AET) which
links the toxicologically relevant concentration to the
observed analytical signals. A significant problem in AET
evaluation is caused by response factor (RF) variation.

Finally, the benefits of this approach for detection of
compounds with little to no mass spectrometry response

In this talk, the use of large UFs for GCMS and LCMS (UF
= 4 and 10 respectively) will be contrasted with the use of
a multidetector approach to AET evaluation. The mul-
detector approach leverages the independence of the
response factors for a given compound obtained on dif-
ferent detectors and chromatographic systems to over-
come potential weak signals on any one detector and
thus reduces the reliance of the method on UF to over-
come response variation. The multidetector approach
was summarized in two recent publications (Jordi et al.
(Jenke and Odufu, Journal of Chromatographic Science
2012;50:206–212). The prominent and necessary use of
surrogate standards for AET evaluation introduces error
into the precise estimation of the signal strength which
corresponds to the toxicologically relevant concentra-
tion. To overcome this problem, an uncertainty factor has
been introduced into the AET equation and regulatory
agencies have provided recommendations as to values
for the UF (GC/MS with UF =4, LC/MS with UF =10). While
this approach does account for response variation, it
also introduces other difficulties including lower AET
values which can be difficult or impractical to achieve
which then require additional sample concentration due
to limited instrument sensitivity. This has the potential to
counteract the perceived benefit resulting in compound
loss or degradation and additional regulatory scrutiny
of the sample preparation process. This approach also
results in a significant potential for false positives (i.e.,
compounds that are below the AET concentration are de-
termined to have a peak area above the threshold associ-
ated with the AET). An alternative approach is therefore
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ISO 10993-18 for medical devices. The first step in the E&L
will be highlighted including demonstration of false negatives using the UF of 4 and 10 strategy.

Afternoon Networking & Coffee Break

3:10 Back to Basics: The Importance of Proper System Suitability and Limit of Detection for E&L Studies

Gyuri Vas, Business Technical Scientific Liaison, Intertek Pharmaceutical Services

Since the AET concept was introduced to the analytical testing of extractables and leachables, the analytical test methods required to have detection capability below to that limit. It was not a challenging task when the AET levels were at or above 100 ppb level, which can be achieved by any laboratory. When the industry moved to lower detection requirements related to large volume parenteral products, however, laboratories faced more challenges. For the E&L data packages, US FDA requires evidence for the performance of the analytical methods used for the testing, and one of the most critical performance parameters is the limit of detection (or LOQ). The ICH method validation guidance (Q2B (R1)), providing guidance for calculating the limit of detection, however, does not provide examples in detail how to execute those calculations. The most common method for LOD assessment is determined by a signal-to-noise calculation, however this approach has significant flaws. Examples related to E&L studies with different AET levels, will be presented to show how an LOD of an analytical method can be appropriately assessed.

3:50 PQRI Safety Thresholds: Putting in Place E&L Best Practices for Parenteral Drug Products

Diane Paskiet, Director, Scientific Affairs, West Pharmaceutical Services

As drug and biological products and their delivery systems become more and more complex, so does the challenge of assessing risks associated with extractables and leachables. The overall concepts for safety thresholds are part of the benefit-risk framework, but the justifications and documentation for the analytical evaluation threshold, extraction conditions, extraction solvents and analysis are critical to ensure the proper data for intended use. This presentation will highlight the current day regulatory environment and various scenarios for developing E&L studies and assessing patient safety.

4:30 Qualification and Risk Assessment of a Single Use System

Chien-Ju (Cherry) Shih, Ph.D. Senior Scientist, Regulatory and Validation Strategy, Pall Corporation

The increasing availability of extractable datasets aligned to standardized protocols (BPOG and USP <665> -low, moderate, high risk) have made it possible to risk assess a complex single-use system (SUS) which consist of multiple components and various materials of construction. A streamlined approach for utilizing existing datasets to support end user qualification of SUSs will be shared, as well as how the aggregate component approach (on paper exercise) compares to a process-specific, simulation solvent approach preformed on the final customized assembly. The benefits, challenges and takeaways from this comparison will be discussed. In addition, modifications and similar approaches that leverage existing knowledge and datasets to risk assess potential future changes to system (e.g., addition of sensor, tubing length, etc.) will be explored.

Happy Hour Mixer

Join your colleagues in the hotel bar for informal networking. Complimentary appetizers provided.

Wednesday, September 21, 2022

Regulatory Spotlight: Implementing ISO 10993 Standards for Med Devices

8:15 Medical Device E&L: The ISO 10993-12 Extraction Conditions Round Robin Study and Its Aftermath

Ted Heise, Vice President, Regulatory & Clinical Services, MED Institute

In 2015, results of a study on ISO 10993–12 extraction conditions raised questions in ISO/TC 194 about adequacy of the conditions for genotoxicity hazard identification. The results spurred formation of a task force that designed and oversaw a round robin study intended to investigate 10993–12 extraction conditions in greater depth. In the study, four laboratories each extracted four materials with a variety of solvents using several different extraction ratios, temperatures, and durations. The resulting extracts were analyzed using instrumental methods widely employed in the E&L field. Unforeseen challenges caused the study to report out only a portion of the planned results; most profoundly, reporting number rather than area of peaks from each analysis. Analysis of these limited data showed no significant trends for any extraction condition; however, solvent polarity was significant.

Despite study limitations, its results provoked considerable concern and several disparate related activities. These included:

- Formation of a new task force in the TC charged with developing a technical report aimed to provide guidance on optimizing quality of extractables studies
A deluge of onerous deficiency questions from regulators reviewing E&L studies of medical devices
Consideration of a potential new round robin study within broader discussions hosted by FDA’s Office of Science and Engineering Laboratories

This session will deliver a high-level overview of the TC 194 round robin study and provide attendees with updates on these listed activities.

8:55
ISO 10993-17: Application of Proposed New Approaches to Facilitate Toxicological Risk Assessment of Medical Devices

Sherry Parker, Senior Director of Regulatory Toxicology, WuXi AppTec

Based on the recently published requirements and recommendations of ISO 10993-18:2020: chemical characterization of medical devices often results in very large numbers of chemicals generated through exaggerated and exhaustive extractions, and the burden of conducting toxicological risk assessments of these large sets of screening data. ISO 10993-17 is currently under revision, soon to be published, and will provide guidance for exposure dose estimation, use of toxicological thresholds, and derivation and evaluation of Margins of Safety for medical device constituents. The proposed revision of ISO 10993-17 also has tools that will reduce the burden of toxicological risk assessment, including the application of toxicological screening limit to prioritize chemicals for toxicological risk assessment, and estimation of exposure to extractable chemicals through assumed or actual release kinetics information for extractable chemicals. This new standard will also serve to identify short-term vs. long term toxicological risks, and this will lead to more practical risk mitigation strategies. An overview of the new revision will be presented, and examples using medical device extractables data will be provided to demonstrate these new approaches.

9:35
Analytical Considerations in Extractables and Leachables Testing of Drug-Device Combination Products

Dujuan Lu, PhD, Manager/Global Leader-E&L, SGS Health Sciences

Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products. Depending on whether the product is intended to submit as a medical device, pharmaceutical drug product, or biological drug product, the requirements in terms of extractable and leachable (E&L) testing could be different. The E&L study designs of pharmaceutical and biological drug products typically follow USP <1663> and <1664> for extractables and leachables associated with pharmaceutical packaging/delivery system. However, E&L testing for medical devices is usually considered as chemical characterization of medical device materials per ISO 10993-18.

This presentation will overview the difference and similarity of E&L requirements between pharmaceutical products and medical devices. The key elements regarding E&L study design of combination products will be discussed. Several case studies on the extractables and leachables testing of combination products will be presented.

Key points to be covered:
- Regulatory & industry guidance to follow for E&L study design of Drug-Device Combination Products
- Difference & Similarity on E&L requirements between pharmaceutical products and medical devices
- Case studies on E&L Testing of combination products

Morning Networking & Coffee Break

10:45
Mitigating Uncertainty in Chemistry Characterization & Toxicological Risk Assessment

Leachables to Extractables Correlation: Noose, Nuisance, Nonsense or Necessity?

Dennis Jenke, Founder & Principal, Triad Scientific Solutions

It all started with a simple concept. If a packaging system is profiled for extractables, presumably as a means of forecasting leachables, and then the packaged drug product is profiled for leachables over shelf-life, logically there will be a strong correlation between the list and amounts of leachables and the list and amounts of extractables. Such a correlation is fortuitous as it serves three useful purposes: (1) verifies the rigor and completeness of the leachables profiling activity (as one does not want to miss leachables during a leachables migration study), (2) allows extractables testing to do the work of leachables testing in activities such as change control (as managing change by testing incoming items for extractables may be simpler and more efficient than testing manufactured drug products for leachables), and (3) supports the premise that extractables data can forecast leachables. But then things got complicated. Extractables and leachables studies were performed and poor correlations were obtained, suggesting (perhaps) that the honorable profession of E&L testing was not being practiced with the expected and necessary high level of scientific competence. In fact, nothing could be further from the truth. In this presentation we are reminded of the underlying aspects of study design and implementation that must be recognized and controlled to enable the effective correlation of leachables to extractables and we remember the logical, and perhaps not so log-
ical, reasons why even under the most equitable and well-controlled experimental circumstances leachables may not be correlatable to extractables.

**11:25**

**Practical Use of Computational Models for the Chemical Characterization and Toxicological Risk Assessment of E&L Compounds Released from Medical Devices**

*Ron Brown, Risk Science Consortium, LLC*

Accurate chemical characterization information and toxicity data are needed to assess the toxicological risks posed by patient exposure to compounds released from medical device materials. However, compound-specific exposure and toxicity data are sometimes lacking for E&L compounds and this lack of data introduces uncertainty into the toxicological risk assessment process. In the absence of the necessary data, computational models can often be used to support the chemical characterization process and to predict the toxicity of the extracted compounds. For example, the nontargeted analysis approach typically used for the chemical characterization of medical devices often results in the presence of unidentified compounds in the extract. The EPA CompTox Chemicals Dashboard will be discussed as a tool to help identify unknowns resulting from nontargeted analysis. There are also challenges associated with estimating the rate at which compounds are released from an implanted device under clinically relevant extraction conditions. Migration models, like the FDA Color Hazard and Risk (CHRS) Calculator, will be discussed as a means to estimate the rate at which leachable compounds, notably, color additives, migrate from implanted devices. To address the lack of compound-specific toxicity data, computational models can be used to fill these gaps for data-poor compounds. Open-source models to predict the potential mutagenicity and carcinogenicity of extracted compounds will be discussed and models to predict other toxicological endpoints, like skin sensitization, will be explored. Finally, the importance of evaluating the accuracy of model-derived predictions using an expert review process is discussed and emphasized.

**12:05**

Complimentary Lunch

**1:15**

**Extractables and Leachables Assessments for Lower Risk Dosage Forms**

*Michael A. Ruberto, President, Material Needs Consulting*

Most of the newly published “best practices” for extractables and leachables (E&L) testing for container closure systems are focused on high-risk dosage forms, such as inhalation, injectable, and ophthalmic drug products. But what are the regulatory expectations for lower risk dosage forms such as oral and topical? Can a “risk-based approach” be used to in designing the E&L testing strategy for these drug products? This presentation will focus on proactive approaches for determining the leachables risk for primary and secondary packaging used with solid and liquid oral dosage forms as well as topical drug products. Some of the discussion topics will include:

- Leveraging the selection of materials of construction for the container closure systems that are regulated for food contact applications according to 21 CFR 174-186 in the design of the extractables testing
- Examples of performing assessments in the form of “paper exercises” versus E&L testing
- Effectively assessing the leachables risk of bottles constructed from various types of polymers
- The impact of closures and corresponding liners and/or induction seals on leachables
- How to efficiently determine the leachables risk of adhesive labels
- E&L study plans for plastic and metal tubes used to package topical drug products
- How to efficiently address post-approval changes to the materials of construction for container closure systems

**1:55**

**Extractables & Leachables Case Study for Cream/Gel Drug Topical Drug Product**

*Eric Hill, Senior Director of Chemistry Laboratories, Boston Analytical*

Topical creams and gels are used to treat dermal conditions, and also incorporate the active ingredient of the drug transdermally into the circulatory system through the skin. Topical products have many applications; however, they present unique leachables concerns compared to traditional drug products. Topical creams and gels typically take the form of an oil-in-water emulsion, which is a very complex matrix to analyze. Extractables studies involve extraction of the packaging components (usually comprised of tubes or pumps) with neat solvents, which must be selected to incorporate the chemistry of the oil-in-water emulsion matrix. Leachables studies must incorporate analysis of the cream or gel material directly for leachables. The complex formulation of the emulsion results in interferences observed during the chromatographic analyses, if prepared using standard liquid-liquid extraction or dilution techniques. Topical products also often have low AET values, due to the high dosage amounts which complicates the challenge of working with this product type. A work flow is presented that gives detailed procedure involving concentration and clean-up to simultaneously achieve the low AET value and remove matrix interference. The resulting samples are analyzed as appropriate for volatiles, semi-volatiles, non-volatiles, and metals with gas chromatography/mass spectrometry (GC-MS), liquid chromatography/mass spectrometry (LC-MS) and inductively coupled plasma mass spectrometry (ICP-MS) to provide comprehensive leachables profiles. Data and the study outline will be presented.

**2:35**

Afternoon Break
Extractables & Leachables Summit 2022

Sample Enrichment Approaches for Extractable and Leachable Studies

**Sam Albeke, LC Manager, VR Analytical**

Extractable and leachable studies are designed with the patient in mind. Therefore, analytical evaluation thresholds (AET) based on thresholds of toxicological concern (TTC as per ICH M7) are calculated in order to determine the minimum analyte concentration required by the analysis. Required limits of quantification are often low ppm to ppb levels but can often be lower. This is close to limit of detector sensitivity. Sample preparation and sample enrichment are critical in achieving the required sensitivity for successful extractable and leachable studies. These approaches are amongst the least considered and understood areas of extractable and leachable program design. We will present different sample preparation approaches for improving analytical sensitivity for non-targeted trace analysis via a range of novel and well-established automated sample introduction techniques. These approaches are particularly important for samples which require detection thresholds which are below the detectors limit of detection/quantification, while overcoming challenges of complex matrices. The following topics will be discussed:

- Key analytical challenges associated with meeting ever decreasing AET’s to assess patient safety
- Overview of novel and well-established sample enrichment approaches
- Case studies highlighting analytical advantages for analytes across the physico-chemical space

USP’s Perspective on the Development of System Suitability Standards for the Analysis of Extractables and Leachables

**Dr. Prabhakar Reddy, Senior Principal Scientist, Team Leader Science, General Chapters, United States Pharmacopeia**

Abstract to come.

Critical Issues Roundtable

Should E&L Reference Standards be Standardized?—A Roundtable Discussion

**Moderator: Michael Eakins, Eakins & Assoc.**

Panelists:
- Christopher Houston, Bausch + Lomb
- Dennis Jenke, Triad Scientific Solutions
- Piet Christiaens, Nelson Labs Europe
- Prabhakar Reddy, USP

Participants:
- The Audience

Close of Program
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