PharmaED RESOURCES, Inc.

Extractables & Leachables West Virtual Summit 2021

Ensuring Quality, Safety, Suitability and Regulatory Compliance for Drugs, Biologics and Medical Devices

November 11–12, Online PST

Featuring Lessons Learned and Case Studies from Industry Experts:

Ted Heise
MED Institute

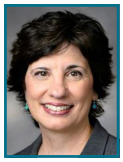
Ping Wang
Johnson & Johnson

James Hathcock
Pall Biotech

Dennis Jenke
Triad Scientific

Sherry Parker
WuXi AppTec

Ron Brown
FDA (retired)

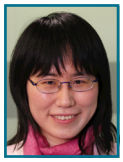


Diane Paskiet
West

Roger Pearson
Aspen Research

Michael Ruberto
Material Needs

Michael Eakins
Eakins & Assoc.



DuJuan Lu
SGS

Jordan Tocher
Jordi Labs

Philippe Verlinde
Nelson Labs

Steve Zdravkovic
Baxter

Eric Hill
Boston Analytical

Emma Leishman
Element Materials Tecchnology

Nicholas Keyes
American Preclinical Services

With Comprehensive Coverage On:

- **Designing and Improving Risk-Based Assessment of E&L Data for Drugs, Biologics, and Medical Devices**
- **Update on Ongoing Revisions to ISO 10993 Standards for Medical Devices**
- **Update on USP General Chapters <87> & <88> for Biological Reactivity Testing & <1031> for Biocompatibility**
- **Regulatory Strategies in the Age of Covid-19: Lessons Learned**
- **AETs and Response Factor Variation for E/L Studies**
- **Meeting Regulatory Expectations for E&Ls in Drug Products, Delivery Systems, and Medical Devices**
- **Overcoming Common Analytical Challenges in E&L Studies**
- **Toxicology Assessment for E&L Studies**
- **E&L Best Practices for Medical Devices & Combination Products**
- **Chemical Characterization in Biocompatibility for Med Devices**
- **E&L Considerations in the Qualification and Validation of Single-Use Systems**
- **Addressing E&Ls from Bioprocessing Equipment & Product Packaging Perspectives**
- **And More!**

Featuring Representation From:

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Nelson Labs A Sotera Health company · Jordi Labs · Boston Analytical · Material Needs Consulting · TRIAD · ASPEN Research · SGS · APS American Preclinical Services · PerkinElmer For the Better

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Thursday, November 11

8:00 

Chairperson's Welcome & Opening Remarks

Spotlight on E/L Risk Assessment—Strategies & Best Practices in the Age of COVID

8:05 **Risk Assessment Strategies of Single Use Systems During the Covid Pandemic—Too Many Materials, Too little Time?**

Ping Wang, Scientific Director, Johnson & Johnson

Many organizations and companies are developing Covid vaccines to combat the virus. Due to the global pandemic, the needs for vaccines are in the billions of doses in the next couple of years and beyond. The demand for the Covid vaccines has put tremendous pressure on the supply of single use systems, and final DP container closure systems, such as vials and stoppers. It is almost impossible to source the SUS or CCS from a single supply due to the shortage. Therefore, it is imperative to be flexible to procure these materials to meet current product demand and increase supply resilience. Dual and multiple sources of materials during the development process or after EUA, and manufacturing at multiple facilities/CMOs are the common approaches in order to meet the demand to control the spread of the deadly virus. However, multi-sourcing and manufacturing also dramatically increased the number of materials and complexity of risk assessment, not to mention the limited time to perform the "normal" testing and assessment due to the health crisis. This presentation will address some novel approaches to assess the risks of SUS and CCS, meanwhile maintaining scientific rigor.

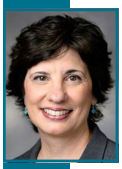
8:45 **Classification and Chemical Safety Qualification of Packaged Drug Products**

Dennis Jenke, Chief Executive Scientist, Triad Scientific Solutions, LLC

During a packaged drug product's lifespan, packaging-related substances might leach into the drug product, potentially adversely affecting the drug product's key quality attributes, including safety. Thus, the packaging is profiled for extractables as potential leachables and/or the drug product is profiled for leachables over its lifespan (chemical characterization), qualifying both as being suited for their intended use. It is reasonable to propose that the extent of chemical characterization depends on the risk that leached substances could adversely affect drug product quality; the higher the risk, the more extensive and rigorous the required qualification. Although regulatory guidance supports and advocates such a risk-based approach to chemical characterization, the existing guidance no longer reflects current regulatory practice. To address this circumstance, this presentation proposes a risk classification process (risk evaluation matrix) for drug products and packaging and a risk-based approach to chemical characterization, establishing chemical characterization requirements for individual risk classes.

9:25 *A Brief Message from our Sponsors/Break*

9:40 **Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables (E/L) for Parenteral Drug Products**



Diane Paskiet, Director of Scientific Affairs, West Pharmaceutical Services

The PQRI recommendations on safety thresholds and best demonstrated practices for E/L in parenteral drug products (PDP) are updated. These approaches will apply to intravenous, subcutaneous, and intramuscular injectable routes of administration. There are unique considerations for the quality and safety of biological products due to potential sensitivity and complex formulations. Recently, the analytical evaluation threshold (AET) has become more complicated due to the recent introduction of an AET specific to a medical device (ISO-10993). PQRI's recommendations for PDPs stem from the contributions of over a hundred industry experts and regulators. When a pharmaceutical product is being introduced to a patient, extractable studies should be designed to guide leachable methods based on risks associated with the specific pharmaceutical product representative and use conditions. The selection of extractions solvents, exposure conditions and analyses should be justified and documented. This presentation will review the PQRI PDP highlights and illustrate extractable approaches for prefilled syringe, small and large volume parenterals.

10:20 **Managing the Risk of Leachables Using an E/L Materials Assessment**

Michael A. Ruberto, Material Needs Consulting, LLC

The extractables and leachables (E/L) best practices provide guidance on defining the extractive power of solvents as well as selecting the extraction techniques that will best simulate or even accelerate the storage conditions for the drug product. However, these best practices are not prescriptive in nature and offer a general strategy or approach for evaluating the risk. In addition, the role of the material of construction in the diffusion process has been less clearly defined. There is limited guidance to proactively select the polymer components that will have the best compatibility with the drug or process stream, to lower the leachables risk. Finally, the expectations of the various regulatory bodies can vary depending on the application or dosage form of the drug product.

The goal of an E/L materials assessment is to evaluate the potential of a material to introduce leachables into a drug product, process stream, or patient before any testing is performed. This assessment report serves as the blueprint or script for evaluating the E/L risk of the materials used to construct the CCS and/or manufacturing equipment.

Most importantly, this document serves as an excellent tool for conveying to the regulatory authorities the over-

all strategy that was used to determine the leachables risk of the CCS and/or manufacturing equipment when submitted with the drug application. This presentation will focus on a step-by-step approach for performing an E&L materials assessment.

11:00 *A Brief Message from Our Sponsors*

11:05 **Uncertainty Factors Reconsidered: Toxicological & Chemistry Perspectives**

Ron Brown (Retired FDA), Toxicologist, Risk Science Consortium, & Dennis Jenke, Chief Executive Scientist, Triad Scientific Solutions, LLC

Inherent in the safety assessment of leachables present in packaged drug products and released from medical devices is a range of uncertainties associated with the either the chemical testing for leachables or the toxicological risk assessment of these compounds. From a chemical testing perspective, uncertainty is present in the three outcomes of such testing, including the discovery of all relevant leachables, the correct identification of the discovered leachables and the accurate quantitation of the identified leachables. From a toxicological perspective, there are uncertainties associated with the quality of the toxicity data, variability in the population response to a chemical compound, differences in potency of compounds in experimental animals to humans, and the clinical relevance of toxicity data from routes and durations of exposure that do not correspond to the intended use of the device or drug product. In this presentation, the speakers will identify sources of uncertainty in the chemical testing and toxicological risk assessment phases of the safety evaluation process and will consider approaches to address and mitigate the uncertainty. The speakers will also consider the impact that uncertainty has on the safety assessment of the product.

11:55 *Complimentary Lunch*

12:55 **PerkinElmer Post-lunch Presentation**

Abstract coming soon

Q&A: Ask the Experts

1:15 **E&L Regulatory Panel Discussion**

Moderator: Michael Eakins, Owner, Eakins & Associates

Panel:

- Dennis Jenke, Triad Scientific Solutions
- Ronald Brown, Toxicologist, FDA (retired)
- Ping Wang, Johnson & Johnson

Discussants: The Audience

Methodological Development in E/L Study Design

1:50 **A Discussion of Several Study Design Considerations Pertaining to the Screening of Substances Extracted and/or Leached from Pharmaceutical Contact Materials**

Steve Zdravkovic, Research Scientist II, Renal Extractables and Leachables Team Baxter International, Inc.

The assessment of substances that can be extracted (extractables) or leached (leachables) from systems that contact pharmaceutical products often starts with a general screening of these substances in relevant samples. Although screening studies may be of a qualitative and semi-quantitative nature, the data they generate are critical in ensuring the suitability of the system(s) used to manufacture, store, and/or administer the product. As such, it is important they are designed using appropriate analytical techniques and methodologies so that representative and reproducible data are obtained. The goal of this presentation is to provide insight into several, but by no means all, good practices for the preparation and analysis of samples in extractable and/or leachable screening studies in order to help ensure representative and reproducible results are ultimately obtained.

2:30 *A Brief Message from Our Sponsors/Break*

2:45 **The Use of Solid Phase Microextraction (SPME) in E/L Studies**

Roger Pearson, President, Analytical Services, Aspen Research Corporation

Common approaches to extractables studies of medical devices or combination products or pharmaceutical closure systems is extraction with a range of solvents (polar, modified polar, and non-polar). Extraction times and temperatures vary but at the end of the extractions one is left with deciding how to analyze the extracts. One of the common analytical techniques is GC/MS for volatile to semi-volatile organics. Often, to reach the desired level of sensitivity, the extracting solvents need to be back extracted (liq/liq extraction) into a different organic solvent which is then volume reduced to concentrate the analytes. An alternative approach is to use Solid Phase MicroExtraction (SPME) and then desorb the SPME fiber via the GC injection port. This has the advantage of not diluting the analytes in a solvent and thus affords superior sensitivity.

We have used SPME-GCMS for various projects including, but not limited to, Extractables and Leachables. This presentation will review the SPME techniques, their advantages and disadvantages, and offer some case stud-

ies relevant to both extractables and leachables studies. Topics touched on will include:

- Use of SPME for vapor phase analyses (HS-SPME-GCMS)
- Use of SPME for liquid phase analyses (Immersion-SPME-GCM)
- Types of fibers
- Representative sensitivities
- Calibration, range, linearity, matrix effects
- Case studies

3:25 *A Brief Message from Our Sponsors*

3:30 **Extractables/Leachables for Cream/Gel Topical Drug Products—A Case Study**

Eric Hill, Director, 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. Example data and the study outline will be presented.

4:20 *End of Day One*

Friday, November 12

8:00 

Chairperson's Welcome & Opening Remarks

8:05 **Materials Impact Assessment of X-ray Sterilization on Single-Use Plastics and Systems Used in Pharmaceutical Manufacturing**

James Hathcock, Senior Director, Regulatory & Validation, Pall Biotech

Sterilization of bioprocessing single-use systems and medical devices relies heavily on cobalt-60-initiated gamma irradiation, which given rapidly increasing demand, is facing marked capacity challenges and business continuity risks. To mitigate these critical security of supply risks, contract irradiators, integrators, and biomanufacturers are working through industry groups such as BPSA and Biophorum to quickly risk assess the impact of X-ray sterilization as a suitable alternative to supplement industry capacity, with the understanding a fully implemented solution is required within the next 2-3 years. As radiation can significantly impact the material properties of plastics as well as their extractables and leachables profiles, a key aspect of the risk assessment is understanding the impact-drivers of gamma and x-ray irradiation on single-use materials, and the extent to which, if any, the profiles may differ. Data will be shared evaluating the fundamental material properties of single-use plastics as well as USP <665> standard component extraction profiles following X-ray or gamma irradiation. The overarching goal is that the community of regulators, suppliers, and biomanufacturers collectively review the risks with adoption of x-ray sterilization and create the right size and quality data packages to enable a rapidly-needed industry solution.

8:45 *A Brief Message from Our Sponsors*

Regulatory Spotlight: Recent USP Chapter Revisions for Drug & Med Devices, and Implementation of ISO 10993-17 and -18

8:50 **Update on USP General Chapters for Biological Reactivity and Biocompatibility**

Michael Eakins, Founder & Principal, Eakins & Associates

The USP Packaging and Distribution Expert Committee (PD EC) formed an Expert Panel in 2015 to undertake a comprehensive revision of the four USP bioreactivity chapters:

- *Biological Reactivity, In Vitro* <87>
- *Biological Reactivity, In Vivo* <88>
- *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* <1031>
- *Sensitization Testing* <1184>

These chapters have a long history with <88> becoming official in 1975, <87> in 1990, <1031> in 2002 and <1184> in 2007. Chapters <87> and/or <88> are referenced in *Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems* <381> that defines the requirements of elastomeric components and in *Plastic Materials of Construction* <661.1> and *Plastic Packaging Systems For Pharmaceutical Use* <661.2> chapters defining requirements for plastic materials of construction and plastic packaging components. Chapter <1031> was written to provide guidance on the use of <87> and <88>.

The USP is evaluating strategies to 1) reduce the amount of redundant testing of existing plastic and elastomeric materials and eliminate unnecessary animal testing for new materials, 2) refine the type of testing performed to align with the potential risk, and 3) replace in vivo testing with in vitro testing or the utilization of other information via a risk-based approach focused on the knowledge of the material and pharmaceutical application. To accomplish this objective the USP would like to expand the number of *in vitro* tests to give end users more tools in the material evaluation process. In <87>, the potential tests for addition are a neutral red uptake cytotoxicity test and four genotoxicity tests.

In <88> the potential areas of omission are:

- Plastic Classes I-VI (Class VI testing to be retained but renamed as Pharmaceutical Grade Polymeric Materials)
- *Implantation Test* (due to the chapter's focus on packaging materials/components, which are not implanted)
- Safety Test for biologics since it is obsolete

Chapter <1031> is revised and is now devoted to the Biocompatibility of Pharmaceutical Packaging/Delivery Systems and Their Materials of Construction. Sensitization testing will be moved into <87>. The presentation will review these proposed changes in detail.

9:25

Implementing 10993-18: Lessons and Challenges from a Year in Print

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

ISO standard 10993-18:2020, Biological evaluation of medical devices—Part 18: Chemical characterization of medical device materials within a risk management process published in January 2020 and has therefore been in print for a little over a year now. Although associated published guidance from regulators is scant, some knowledge related to their expectations is beginning to emerge.

Firstly, in July 2020, FDA published the extent of their recognition of this new version of the consensus standard. Although part 18 is largely recognized, there are a few sections that the Agency does not recognize. In this presentation, these six short specific sections will be discussed—along with the presenter's understanding of the reasoning for their non-recognition.

Secondly, over the past year both FDA and Notified Body reviewers have started to make their thinking known through presentations at scientific conferences. Reviewer preferences in the use of 10993-18:2020 have also begin to emerge, through deficiency questions and non-conformities issued against marketing authorization applications. In addition to his experience from interacting with regulators in developing the new standard, the presenter will draw on experience in supporting sponsors dealing with some of these challenging regulatory reviews.

General topics to be covered include the following:

- When knowledge of device materials of construction and their composition may be adequate, and when chemical analysis may be required
- In chemical analysis, which instruments are expected as well as considerations in the overall analytical approach, such as:
  - Solvent selection, especially for nonpolar solvents
  - Setting the AET (e.g., selecting uncertainty factors and a dose-based threshold)
  - Dealing with sample manipulation (e.g., concentrating or solvent exchange)
  - Selection of internal and surrogate standards
  - Issues with assigning compound identities to unknown analytical peaks

Attendees are expected to come away from this session with an improved awareness of the current pitfalls in chemical characterization of medical devices, as well as a better understanding of best practices in this developing field.

10:00 *A Brief Message from Our Sponsors/Break*

10:15

Analytical Considerations in E/L Studies of Medical Devices per ISO 10993-18

Dujuan Lu, Ph.D. , E&L Manager/Global Leader, SGS Life Sciences

Chemical characterization (Extractable and Leachable Studies) per ISO 10993 has become an important component of biocompatibility testing for medical devices. A major revision of ISO 10993-18 "Chemical characterization of medical device materials within a risk management process" was recently published in the beginning of 2020. This presentation will focus on the analytical considerations of medical device extractable and leachable (E&L) studies per the new ISO 10993-18 chapter. Topics to be covered will include:

1. Understand the analytical testing requirements per the new ISO 10993-18.
2. How to design an extractable study of medical devices in terms of solvent selection, extraction conditions, setting the suitable analytical evaluation threshold (AET), etc.
3. Analytical case studies per common regulatory deficiency points on medical device E&L studies, including requirements on reference standards during semi-quantitation, spiked recovery, analytical uncertainty factors, and compound identification status.

10:50 **Updates on ISO 10993-17, Toxicological Risk Assessment of Medical Devices: Tools and Tips for Handling Large Amounts of Chemical Characterization Data**

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 device materials within a risk management process, and regulatory expectations for chemical characterization of medical devices, the outcome of chemical characterization is often very large numbers of chemicals that need to be assessed by the toxicologist in the toxicological risk assessment. ISO 10993-17 is currently under revision to provide tools for the toxicologist to interpret these chemical characterization data to better and more consistently support medical device safety. Recent updates to draft ISO 10993-17 will be provided in addition to strategies for handling large amounts of chemical characterization data, including organization, work flow and risk mitigation.

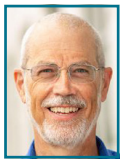
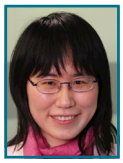
11:25 *A Brief Message from Our Sponsors*

Q&A: Ask the Experts

11:30 **ISO 10993 Panel Discussion**

Moderator: Michael Eakins, Eakins & Associates

Panel:


- Ted Heise, MED Institute
- DuJuan Lu, SGS
- Sherry Parker, WuXi AppTec

Discussants: The Audience

12:10 *Complimentary Lunch*

1:10 **Eurofins EAG Post-Lunch Presentation**

Abstract coming soon

Critical Issues—Achieving Proper Identification in GC/MS Mass Spectral Matching Protocols

1:30 **The Strengths and Pitfalls of a GC/MS Identification Strategy Based Upon Mass Spectral Matching Using NIST and Wiley Mass Spectral Libraries**

Dr. Philippe Verlinde, Mass Spectrometry Expert in the Hercules R&D Team, Nelson Labs

When establishing an extractables profile for a material, one of the most important steps in the process is to identify every single peak in a chromatogram as accurately as possible. A correct identification of extractable compounds is one of the most important actions to take when characterizing the extractable profile, as it is only with a correct identification that one can link the identity of the compound to its relevant toxicological information.

In GC/MS (either via a Headspace or a Direct Injection inlet), all labs (including Nelson Labs) that are performing extractables studies rely—to a greater or lesser extent—on publicly available commercial MS libraries (such as NIST or Wiley) to assist in the identification process. Indeed, the quickest way to identify a GC/MS mass spectrum is to verify if the mass spectrum is present in the commercial library, as a Mass Spectral Matching (MSM) strategy will allow to immediately link a mass spectrum to the compound's identity.

However, improper use of these commercial MS-libraries may lead to incorrect or flawed identifications of extractables, which may compromise the subsequent toxicological evaluation. As there is no subsequent "quality control" on the identification of compounds anymore, it's the responsibility of the analytical lab to correctly attribute a level of identification for the compound based upon MSM, this to avoid reporting of misidentified of compounds.

The presentation will address the following issues:

- What are MSM factors, how are they determined, and what value do they have?
- How to verify if a compound is present in a commercial MS-library. If a compound is not present in a MS-library, the identification strategy of MSM will always fail.
- Which values can give a reliable identification via MSM, and which values are too far off for any reliable identification?
- What to do if the quality of the MSM does not allow for an unequivocal identification.
- How can a review process of the MSM factors help as a "nonsense filter" when reporting identifications.
- The value of a "retention index," information that is often present in commercial MS-libraries, as an additional verification parameter.
- How to broaden this towards more robust identifications in LC/MS?

2:10 *A Brief Message from Our Sponsors*

2:15 **Extractables & Leachables Studies of Electronic Nicotine Delivery Systems**

Emma Leishman, Technical Manager, Advanced Analytics, Element Ann Arbor (Co-authors: Amanda Neely, Derek Beauchamp, and Andrew Kolbert)

The FDA has recently released and required a Pre-Market Tobacco Applications (PMTA) for e-liquids and Electronic Nicotine Delivery Systems (ENDS), or vaping devices manufacturers. Part of the PMTA requires extractables and leachables (E&L) studies. We will discuss the approach, as well as results for the E&L testing on vaping devices for e-liquids. These products provide unique challenges in E&L design because the device is

a delivery system. While similar to the metered dose inhalers (MDIs) of the PQRI Guidance, these devices have a daily usage an order of magnitude higher, which drives AETs lower than for MDIs. They have a comparable number of components, but are manufactured in most cases without regard to pharmaceutical or medical grade materials. The device itself is not only primary packaging for the e-liquid, but also its delivery system, which involves a heated vaporization via one component (a battery) into the consumer's mouth and lungs. In several devices, we have found limited isolation of compartments of the device potentially exposing the battery itself to the e-liquid, which presents a unique leaching issue. Finally, the e-liquid is a propylene glycol/glycerin base whose leachable profile is not well modeled by extractables in either water or isopropanol. We will present data from multiple different devices for which these studies were performed and submitted in support of a PMTA application.

2:55 *A Brief Message from Our Sponsors/Break*

Critical Issues—UF Mitigation and Simulated Use Conditions for Med Devices

3:05 **Update on the Multidetector Strategy for UF Mitigation and the Use of Binary Solvent Mixtures to Simulate the Use Condition for Medical Devices**

Jordan Tocher, PhD, Senior Chemist & Study Director, Jordi Labs

One of the most difficult aspects of chemical characterization for medical devices is the inability to exactly simulate biological use conditions. In chemical characterization of pharmaceutical packaging, a true leachables assessment can be performed by a direct analysis of the drug product. Unfortunately, there is no simple analytical solution which is a direct simulant for the biological environment of a medical device. A similar problem sometimes exists for pharmaceutical packaging when a drug product matrix is so complex that it interferes with the analytical chemist's ability to identify unknown leachables. In this case, the guidance documents have allowed for the application of a simulated drug matrix which is more analytically feasible. This can be reasonably done since the drug matrix chemistry is well understood. For medical devices, this process is not as simple since the biological matrix is so complex. The simulating solvent applied for many externally communicating medical devices has historically been saline. However, a consideration of the biological environment suggests that some medical devices may experience more hydrophobic conditions which could result in greater extraction potential (i.e., adipose tissue). It is also speculated that the components present in blood such as proteins and phospholipids may result in enhanced extraction as compared to saline. For these reasons, the industry has historically relied on water/alcohol mixtures as the go to method to enhance the hydrophobicity of the simulating solvent. Recently, a number of potential concerns have been raised about the use of binary solvent mixtures such as preferential absorption of the more hydrophobic component of the solvent by the medical device. In this talk, we will review the issues related to the use of binary solvents as well as relay results showing a comparison of the extraction power of blood contrasted with saline and water/alcohol mixtures for a series of analytes relevant to blood contacting medical devices. Methods for confirming the absence of preferential absorption of the hydrophobic component of the binary solvent mixture will also be described.

In addition, a brief update will also be provided on the latest work on mitigating the need for uncertainty factors through a multidetector strategy. Response factor variation is one of the major sources of quantitative error in extractables and leachables analysis. This presentation will show the most recent results on the percent coverage for individual detectors (GCMS, LCMS, UV, CAD, and FID) contrasted with combined detector strategies (multidetector strategy) as a function of the UF. These results were recently published in a work entitled "An Analytical Strategy Based on Multiple Complementary and Orthogonal Chromatographic and Detection Methods (Multidetector Approach) to Effectively Manage the Analytical Evaluation Threshold (AET) " (Jordi, M., Heise, T., PDA, 75, 2, 2021).

3:45 **Relative Response Factor and Uncertainty Factor Considerations for Non-Linear Detectors used in Extractables and Leachables**

Nicholas Keyes, Study Director & Principal Analytical Chemist, American Preclinical Services

Recent publications and regulatory guidance documents have emphasized the importance of utilizing an uncertainty factor for adjustment of the AET. The uncertainty factor captures the variation in response between different compounds at a given concentration, determined from a database of relative response factors (RRFs).

Meanwhile, quantitation in extractables and leachables is typically carried out using mass spectrometers, supplemented by one or more additional detectors. These detectors have an expected linear dynamic range based upon the inherent chemistry involved. Lacking experimental data for every possible chemical entity that might be observed in an extractables and leachables study, the implied linearity impacts assumptions behind single-point RRF assessments used to generate uncertainty factors, and whether they are sufficiently protective, or even over-protective.

This presentation presents RRF results for ThermoScientific GC/MS and LC/Orbitrap platforms for chemical characterization, and compares/contrasts those data with results from comparable instrument platforms performed on Agilent systems from literature. It also presents a concentration-dependent approach to RRFs, stemming from non-linear responses, and the potential impact on uncertainty factor corrections and quantitation.

4:25 *Close of Program*

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About your conference destination:

Located in Mission Valley, the Marriott San Diego Mission Valley is the ideal gateway to experience the best of San Diego. Enjoy easy access to San Diego State University, SDCCU Stadium (formerly Qualcomm), Old Town, or hop on the Rio Vista Trolley and explore Mission Bay, SeaWorld, and Downtown San Diego including PETCO and Gaslamp District. See our refreshed meeting spaces including our all-new event lawn ideal for memorable outdoor gatherings. Enjoy a host of amenities and services, from views and casual dining at DEN to our fully equipped fitness center and outdoor pool with a waterfall. Well-appointed guest rooms and spacious suites offer 55" SMART TV's, high-speed Internet and balconies and are perfect for groups visiting San Diego. You will appreciate our Mission Valley hotel's unmatched charm and sophistication.

Registration Information

Register for the conference using one of three options:
Online: www.pharmaedresources.com **Phone:** (217) 721-5774
Mail: 2810 Robeson Park Drive, Champaign, IL 61822

Please Complete the Following

FIRST NAME: _____

LAST NAME: _____

TITLE: _____

COMPANY: _____

ADDRESS: _____

ADDRESS: _____

CITY: _____ **STATE:** _____

ZIP: _____ **COUNTRY CODE:** _____

OFFICE PHONE: _____

MOBILE PHONE: _____

FAX: _____

E-MAIL: _____

VENUE INFORMATION:

Dates:	November 11–12, 2021
Venue:	Marriott San Diego Mission Valley
Venue Address:	8757 Rio San Diego Drive San Diego, CA 92108
Venue Phone:	(619) 692-3800

Please register me for:

Extractables & Leachables West Coast Summit 2021

Standard Registration:	**$1,595**
Early Bird Registration (by September 21):	**$1,395**
Call for government, academic or non-profit rate	

PAYMENT METHOD

CREDIT CARD REGISTRATION:

☐ CREDIT CARD ☐ VISA ☐ MASTERCARD ☐ AMEX

NAME: _____

CARD #: _____

EXPIRATION: ____ / ____

SIGNATURE: _____

BILLING ADDRESS: _____

CHECK REGISTRATION:

To pay by check, please provide a purchase order below. Please note that all payments must be received five (5) days prior to the conference to ensure space. Attendees will not be admitted to the conference without full payment.

PURCHASE ORDER #:

PLEASE NOTE:

PharmaEd Resources does not offer refunds. However, if you cannot attend after registering, we are happy to apply your registration fee to another PharmaEd Resources event, or transfer your registration to a colleague. Notice of cancellation must be received at least 5 days prior to the event.