

# Extractables & Leachables Summit 2020

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

July 30–31, 2020, Wyndham Philadelphia Historic District

*Featuring Lessons Learned and Case Studies from Industry Experts:*



**Mike Eakins**  
Eakins & Assoc.



**David Saylor**  
FDA



**Ted Heise**  
MED Institute



**Ping Wang**  
Johnson & Johnson



**Berk Oktm**  
FDA



**Dennis Jenke**  
Triad Scientific



**Sherry Parker**  
WuXi AppTec



**Lisa Olson**  
NAMSA



**Ron Brown**  
FDA (retired)



**Carsten Worsøe**  
Novo Nordisk



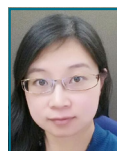
**Charles Felice**  
Janssen R&D



**Mike Ruberto**  
Material Needs



**James Hathcock**  
Pall Biotech



**Cherry Shih**  
Pall Life Sciences



**Mark Jordi**  
Jordi Labs



**Piet Christiaens**  
Nelson Labs



**Steve Zdravkovic**  
PPD



**Roberto Menzel**  
Sartorius Stedim



**Eric Hill**  
Boston Analytical



**Stephen Doherty**  
Toxikon



**Daniel Norwood**  
Feinberg Norwood & Assoc.

## *With Comprehensive Coverage On:*

- CDRH Scientific Perspective on Chemical Analysis for Medical Devices
- ISO 10993-18: Key Concepts and Practices for Effective and Compliant Chemical Characterization Supporting the Biological Evaluation of Medical Devices
- Understanding the Major Revisions to ISO 10993 and the New European Medical Device Regulations
- Case Study: Medical Device Toxicological Risk Assessment Following New Principles of ISO 10993-17
- Identification and Evaluation of Material Quality Attributes (MQA) of Polymeric

- Used in Cell Therapy Products Manufacturing
- Chemical Interactions between Leachables and Biopharmaceuticals
- The Need to Identify Unknowns from a Toxicological Perspective
- BPOG E&L for Single-Use Systems – The Final Chapter
- Utilizing BPOG data for selection and qualification of Single Use Systems
- Extractables/Leachables Studies: Are You Certain About that Uncertainty?
- Reducing Response Factor (RF) Variation and the need for Uncertainty

- Factors (UFs) in Extractables and Leachables Analysis
- Comparison of the Solubilization Properties of Polysorbate 80 and Isopropanol/Water Solvent Systems for Organic Compounds Extracted from Three Pharmaceutical Packaging Configurations
- Comprehensive Extractables Study of Autoclavable Polyethersulfone Filter Cartridges
- Physics-based Model to Predict Patient Exposure to Polymer Additives in Medical Device Materials
- And Much More!

## *With Representation From:*



# Pharma Ed's Extractables & Leachables Summit 2020 is Sponsored by:



**Thursday, July 30**

7:30

*Registration & Complimentary Breakfast & Chairperson  
Mike Eakins' Welcome*

### **Regulatory Spotlight – Chemical Analysis for Medical Devices**

8:10

#### **CDRH Scientific Perspective on Chemical Analysis for Medical Devices**

**Berk Oktem, Chemist, FDA**

Abstract Coming Soon



### **Critical Issues – Identifying Unknowns in E/L Studies**

8:55

#### **The Need to Identify Unknowns from a Toxicological Perspective**

**Ron Brown, Toxicologist FDA (retired)**



When conducting a toxicological risk assessment of extractable and leachable (E&L) compounds, it is typically assumed by the toxicologist that the extracted compounds have been identified with a high degree of certainty. However, because of analytical chemistry challenges, identification of the compounds to this level of certainty is not always possible, especially for non-targeted extractables. This talk will explore the implications of conducting a toxicological risk assessment of compounds that have been only tentatively identified and will evaluate recent proposals to evaluate the safety of unidentified and partially identified E&L compounds. Among the strategies to be addressed in this presentation are the appropriate use of Threshold of Toxicological Concern (TTC) values to serve as default TI or PDE values for compounds that have not been confidently identified and need to identify when a compound is expected to be found in an extract based on knowledge of the composition of the polymeric materials of construction of the device or pharmaceutical packaging.

9:35

*Coffee & Networking Break*

10:00

#### **Extractables/Leachables Studies: Are You Certain About that Uncertainty?**

**Dennis Jenke, President,  
Triad Scientific Solutions**



There are many well-established and well-articulated expectations for extractables profiles including that all extractables above the AET be discovered, correctly identified and accurately quantified. A fundamental expectation that has rarely been articulated until recently is that the extractables profile be reproducible. That is to say that if a test article were provided to several expert testing laboratories, the extractables profiles reported by those laboratories would be similar, if not equivalent, in their important details, including the number of extractables reported and the identities and concentrations of the reported extractables.

Recent, largely anecdotal, evidence suggests that this expectation of reproducibility could be more a wish than a reality and that extractables profiles can vary, in some cases quite substantially, from lab to lab and possibility even within a lab. If this lack of consistency is true and real, it could have a significant bearing on, for example, the use of chemical characterization in the biocompatibility assessment of medical devices.

In this presentation we will examine the published and available literature and data that is relevant to this topic to establish whether the perception is reality and, if so, to consider actions that either amplify or reduce/control variation. Furthermore, the available literature and data will be used to quantify reasonable expectations for reproducibility.

10:40

#### **ICH E&L Guidelines Update**

**Carsten Worsøe, Principal Scientist,  
Novo Nordisk**



The International Committee for Harmonisation (ICH) has approved the procurement of an ICH E&L guideline. Although it is very early in the ICH process this short presentation will give background and history for the topic approval in ICH as well as the currently known process for the ICH guideline.

### **Q&A: Ask the Experts**

10:50

#### **E&L Regulatory Panel Discussion**

**Moderator: Michael Eakins, Owner, Eakins  
& Associates**



Panel:

- Dennis Jenke, Triad Scientific Solutions
- Ronald Brown, Toxicologist, FDA (retired)
- Berk Oktem, Chemist, FDA

Discussants: The Audience

11:20

#### **Reducing Response Factor (RF) Variation and the need for Uncertainty Factors (UFs) in Extractables and Leachables Analysis**

**Dr. Mark Jordi, President, Jordi Labs**



Chemical characterization per ISO 10993 has become an important component of biocompatibility testing of medical devices. Similarly, pharmaceutical packaging is characterized for extractables and leachables to verify the safety of drug products per USP <1663> and <1664>. A major concern regarding the accuracy of extractables and leachables studies is quantitative error due to response factor (RF) variation. This error occurs because many extractables do not have commercially available standards and equal concentrations of different extractables give different signal responses using mass spectrometry detectors. Recent publications have highlighted the risks posed by RF variation for both LCMS and GCM. The importance of this issue has been recognized by the FDA resulting in the addition of an uncertainty factor (UF) in the calculation of the analytical evaluation

threshold (AET). While this aids in mitigating the risks of under reporting of extractables, the resulting revised AET creates significant analytical challenges often exceeding the limit of detection (LOD) of current mass spectrometry instrumentation and requiring sample concentration. It also creates questions as to the validity of risk assessments based on relative quantitation values and is one of the key issues at the root of poor reproducibility in recent high profile interlaboratory studies. It is therefore strongly desirable to define improved methods for quantitation with more universal RFs which mitigate the need for UFs. In this presentation, alternative strategies for quantitation using triple detection liquid chromatography mass spectrometry (LCMS) with ultraviolet (UV) and charged aerosol detection (CAD) as well as Gas Chromatography Mass Spectrometry (GCMS) with simultaneous Flame Ionization Detection (FID) will be presented. Data comparing the response factors a variety of extractables by UV, MS, FID and CAD will be presented demonstrating an approach to reduce overall RF variation, the associated need for UFs and increasing confidence in the resulting risk assessments.

12:00 Complimentary Networking Lunch

1:00 **Identification and Evaluation of Material Quality Attributes (MQA) of Polymeric Used in Cell Therapy Products Manufacturing**



**Ping Wang, Director, Johnson & Johnson, and Charles Felice, Principal Scientist, Janssen R&D**



Cell therapy drug products such as CAR-T present unique challenges with respect to polymeric material risks compared with more common biologic processes. The manufacturing process of cell products has fewer purification steps, resulting in fewer opportunities to remove polymeric-related impurities such as particles, endotoxins, bioburden, and leachables & extractables.

These attributes are material quality attributes (MQAs) that must be assessed and, if the risk is high, mitigated. This presentation will discuss the correlation of manufacturing processes and MQAs, and how these processes will impact the risk levels of the MQAs to the final drug product quality and patient safety. The MQA risk levels of the polymeric at each step will be discussed.

**Research Spotlight – Single Use Systems & BPOG**

1:40 **BPOG E/L for Single Use Systems – The Final Chapter**



**Carsten Worsøe, Principal Scientist E&L, Novo Nordisk, and James Hathcock, Senior Director, Regulatory and Validation Consulting, Pall Biotech**



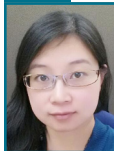
In this presentation, we will cover the following topics:

- Supplier and end-user collaboration
- Extractables ecosystem
- Data review process
- Extractables protocol update
- Community of practice

**Case Studies – Utilizing BPOG data for selection and qualification of Single Use Systems**

2:20

**Utilizing BPOG Data for Selection and Qualification of Single Use Systems**



**Cherry Shih, Senior Scientist, Pall Life Sciences**

The increasing availability of extractable datasets aligned to standardized protocols (BPOG and USP <665>/<1665>) has led to a deeper understanding of extractable profiles in different solvents. We will share cases where specific solvent profiles from BPOG or USP <665> can be leveraged to best support and simplify the risk assessment process, for both, the purpose of initial materials selection as well as qualification of a multi-component single use system in a defined manufacturing process. In applying standardized datasets, we share examples of how extractables profiles performed at different surface area to volume ratios (0.4 to 18 sq.cm/mL) compare to theoretically scaled values based on surface area and volume alone. The goal of these case studies is to simplify and strengthen approaches to qualification of single use materials.

3:00

Coffee & Networking Break

3:25

**Comprehensive Extractables Study of Autoclavable Polyethersulfone Filter Cartridges**



**Roberto Menzel, Laboratory Supervisor, Extractables & Leachables, Sartorius Stedim**

Sterile filters are ubiquitous in biopharmaceutical manufacturing processes. They are in direct contact with the process fluid, and the profiling of the extractables is of high importance, especially in process steps “close to patient” such as single-use final fill. The talk will compare and discuss the extractables profiles of sterilizing-grade 0.2 µm polyethersulfone membrane filter cartridges from different vendors. Pure ethanol and purified water were used as extraction media. Several orthogonal analytical techniques such as HS GC-MS and GC-MS and LC-HRMS in combination with ICP-MS for single analyte detection and the sum parameters total organic carbon, non-volatile residue, conductivity, and pH were used to obtain a most comprehensive extractables profile. Various extractables were found such as antioxidants and degradation products thereof, hydrocarbons, and processing aids. The identified compounds can all assigned to the materials of construction, such as plastic parts or membranes. Focus is given also on the challenges one encounters in Extractables screening studies for example in the analysis of hydrophilizing agents. A basic toxicological evaluation for material safety assessment will be presented showing the overall low risk of the extractables toward patient safety.

4:05

### Assessing the Reactivity of Leachables with Biopharmaceuticals, Using INSULIN as a Marker Compound Combined In-Silico Model with Experimental (Analytical) Verification of Proof of Concept, using INSULIN as a Marker Compound



**Piet Christiaens, Scientific Director, Nelson Labs Europe**

In the EPREX case, leachable induced immuno-responses caused severe adverse reactions to CKD patients. Although the EPREX case is often referred to by the E/L community to stress the importance of an in-depth E/L evaluation of the C/C-system, it also showed that the traditional E/L approach for container/closure systems may not always be adequate in predicting leachables could chemically modify proteins, potentially causing immunogenicity through the formation of "anti-drug-antibodies."

The FDA Guidance for Industry: "Immunogenicity Assessment for Therapeutic Proteins" (2014) describes anaphylaxis, cytokine release syndrome, infusion reactions, non-acute reactions and cross-reactivity to endogenous proteins as the associated safety concerns when considering immunogenicity as a result of chemical interaction between leachables and proteins.

The presentation will address two ways of predicting if any of the chemical compounds, found in the extraction profile of container/closure component, could lead to a chemical interaction if any of those extractables would become a leachable: (1) how to perform an in-silico reactivity approach of a very broad set of commonly known extractable compounds and (2) a chemical reactivity test to actually screen for residual chemical reactivity.

In addition, a chemical reaction model, based on Insulin as a marker compound was developed to actually verify the in-silico predicted chemical reactivity and compare the outcome of the in-silico exercise with the observed reactivity between a predefined set of extractables and insulin.

4:45

### Standard Methods for Extractables/Leachables Profiling: What are the Implications?



**Daniel Norwood, Principal Consultant, Feinberg Norwood & Associates**

Modern analytical chemistry, in the form of GC/MS and LC/MS, has been at center stage in extractable/leachable assessment since the late 1980s. Various organizations (PQRI, USP, etc.) have attempted to establish the basic scientific principles for accomplishing extractables/leachables assessments along with the use of these highly sensitive and selective analytical techniques. Over the past ten years or so, a general consensus has been established regarding the suite of analytical techniques applied to any assessment based on the volatility and chemical nature of the anticipated analytes. This consensus includes: Head-space (HS) GC/

MS for volatile analytes, Direct injection (DI) GC/MS for semi-volatile analytes contained in solvent extracts, Direct injection LC/MS for non-volatile analytes contained in solvent extracts, and ICP/MS for elemental analytes. The consensus does not include all of the details of the analytical methods since the organizations that agreed on best practices did not want to be proscriptive. This presentation will attempt to discuss the possibility of establishing standard methods for extractables/leachables. It will describe the requirements for standard methods along with the implications for the pharmaceutical industry of the implementation of standard methods. The experience of the environmental industry with standard methods in the 1970s and 1980s will be considered.

5:20

*End of Day One*

## Friday, July 31

8:00

*Complimentary Breakfast*

### Critical Issues—Exploring the Major Revisions to ISO 10993-1, -17, & -18: Methodological & Toxicological Considerations

8:30

#### Toxikon Presentation



**Stephen Doherty, Associate Director, Analytical Chemistry, Toxikon**

Abstract coming soon

9:00

### ISO 10993-18: Key Concepts and Practices for Effective and Compliant Chemical Characterization Supporting the Biological Evaluation of Medical Devices



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

The ISO 10993 series of standards on biological evaluation of medical devices has been evolving over the years, working to keep up with progress in knowledge of the subject matter. In keeping with this progress, an update of ISO 10993-1 (the top-level standard) published in 2018. A key change in this revised document was the addition of a more explicit requirement for chemical characterization of all device types—regardless of the nature and duration of patient contact.

To meet the heightened focus on chemical characterization—and to update the existing standard—a major revision of ISO 10993-18 "Chemical characterization of medical device materials within a risk management process" was undertaken. The revised document should publish in early 2020. This conference session will focus on key parts of the new document, bringing in experience and lessons learned from multi-stakeholder development of the final standard.

Topics to be covered will include:

- Navigating the flow chart, including factors that can help determine whether compositional information may be adequate for chemical characterization, or analytical testing of extracts is likely to be necessary;
- Considerations for determining extraction conditions; namely, solvent selection, temperature, duration, and nature of extraction (e.g., simulated use, exaggerated, or exhaustive);
- Distinctions between extractables and leachables in the application of established E&L principles to medical devices;
- Approaches to performing an exhaustive extraction, as well as discussion of how multiple steps can facilitate use of practical safety thresholds;
- Qualification of analytical methods, including discussion of parameters that may be candidates for use; and,
- Additional insights drawn from regulator input during numerous discussions of various elements of the standard.

9:35

### Case Study: Medical Device Toxicological Risk Assessment Following New Principles of ISO 10993-17



**Sherry Parker, Senior Director of Regulatory Toxicology, WuXi AppTec**

ISO 10993-17, which was last revised in 2002, has undergone a significant revision and the proposed title is "Toxicological Risk Assessment of Medical Device Constituents". The revised standard will expand from current guidance on establishing allowable limits of leachable substances, to conducting a toxicological risk assessment of medical device constituents. Proposed updates to the standard and its current status will be presented. Topics will include hazard identification, exposure assessment, dose-response assessment, and risk characterization. There will be emphasis on the use of expert judgement to determine whether the toxicological risks of exposure to extractable or leachable chemicals in medical devices are acceptable, what additional steps may be taken to mitigate risk, including whether exposure estimates could be further refined through additional chemical characterization and when to recommend risk control. In addition, the technical specification ISO/TS 21726:2019, Application of the Threshold of Toxicological Concern (TTC) for Assessing Biocompatibility of Medical Device Constituents, will be discussed. A case study will be presented to provide examples to demonstrate the application of the new principles proposed in ISO 10993-17 and ISO/TS 21726 to the toxicological risk assessment of medical devices.

10:10

*Coffee and Networking Break*

### Q&A: Ask the Experts

10:35

#### ISO 10993 Panel Discussion



**Moderator: Michael Eakins, Eakins & Associates**

Panel:

- Stephen Doherty, Toxikon
- Ted Heise, MED Institute
- Sherry Parker, WuXi AppTec

Discussants: The Audience

11:15

#### Commercial Implications of a Properly Planned Biological Evaluation Strategy, Including the Use of Chemical Characterization



**Lisa Olson, Vice President — North American Laboratory and Global Analytical Services, NAMSA**

Since 2009, the emphasis on a risk management process and characterization of materials continues to shift the biological safety paradigm. Put simply, the days of medical product manufacturers simply contracting with a testing laboratory to perform a handful of biological safety tests is no longer an accepted practice by any global regulatory body. Medical device regulators are requiring carefully planned evaluation strategies based on risk and empirical data.

Join this session to learn how a well-planned strategy utilizing chemical characterization can have favorable and even cost saving implications for the commercialization of your product. This session will be a start to finish, step by step instruction on when to start your planning, what steps to follow to execute chemical characterization testing and/or biological testing, and how to keep your timelines as short or shorter than when performing conventional biological testing.

12:00

*Complimentary Networking Lunch*

1:00

#### Physics-based Models to Predict Patient Exposure to Medical Device Leachables



**David Saylor, Materials Scientist, FDA**

The materials that comprise medical devices contain substances that can be transferred to patients. Patient exposure to these substances may be desirable, e.g. drug delivery, but more generally, there is concern for adverse effects if a chemical is released in sufficient quantities. Historically, the likelihood for adverse effects has been evaluated using animal testing. Toxicological risk assessment (TRA) is an alternative approach that can obviate the need for extensive animal testing. TRA relies

on exposure estimation, yet exposure data are challenging to obtain and interpret. Physics based mass transport models provide a promising alternative to establish clinically relevant exposure estimates. This presentation will provide an overview of exposure models and their use in biological risk evaluation of medical devices, including: potential benefits and current use in regulatory applications, types of models that can inform TRAs, challenges with use in regulatory decision making, and strategies to overcome these challenges.

1:55

### Managing the Risk of Leachables through Proactive Material Selection and



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

Abstract coming soon

2:35

### Coffee & Networking Break

2:50

### Extractables Screening of Single Use Components for Qualification



**Eric J. Hill, Director, Boston Analytical**

Single Use Systems (SUS) present challenges with regards to extractables and leachables, however their ease of use, quick change out capability, cost, and configurational flexibility provide significant advantages over traditional manufacturing set-ups. With these challenges regarding E&L, much attention has been paid to extractables data generation for use in vendor and material selection. Ongoing discussions in the industry revolve around the BioPhorum Operations Group (BPOG) Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing and the proposed USP <665> monograph for single use systems. Regardless of how these discussions resolve amongst the industry, after an SUS is selected there is still testing that must be performed. The data generated during selection is often not robust enough for qualification of the SUS materials for use in the manufacturing setting. It is critical to perform extractables testing of the SUS for material

compatibility using the manufacturing conditions of use, including time and temperature. This extractables testing also should be performed using the actual solutions contacting each SUS material. Case study examples of extractables testing for material compatibility and qualification will be presented.

3:30

### Comparison of the Solubilization Properties of Polysorbate 80 and Isopropanol/Water Solvent Systems for Organic Compounds Extracted from Three Pharmaceutical Packaging Configurations



**Steve Zdravkovic, Senior Research Scientist,  
PPD**

It has been reported that the presence of polysorbate 80 in a pharmaceutical product's formulation may increase the number and/or amount of impurities leached from materials used during its manufacture, storage, and/or administration. However, it is uncertain if/how the solubilization properties of this surfactant compare to non-surfactant solvent systems. The goal of this study is to provide insight into this area of uncertainty by comparing the solubilization properties of polysorbate 80 to those of isopropanol/water solutions while in contact with a plasticized polyvinylchloride parenteral delivery bag, a single-use type manufacturing bag, and a polypropylene bottle. These properties were determined via a binding experiment, in which a set of model compounds was introduced into the solutions, and via an extraction experiment, in which compounds were extracted from the packaging material by the solutions. In both experiments, the amount of each compound present at equilibrium was assayed to determine the extent they were solubilized by the solution from the packaging material. Results from these experiments illustrate differences in the magnitude of solubilization obtained from solutions containing polysorbate 80 as compared to those composed of isopropanol/water. However, it was also demonstrated that their solubilization properties can be linked via a mathematical model.

4:10

### Close of Program



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Venue/Hotel: **Wyndham Philadelphia  
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### **Extractables & Leachables Summit 2020**

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