PharmaED RESOURCES, Inc.

Extractables & Leachables West 2023

November 2-3, 2023, La Jolla CA

Featuring Lessons Learned and Case Studies from Industry Experts:

G. Prabhakar Reddy
US Pharmacopeia

Ping Wang
Janssen

Dennis Jenke
Triad Scientific

David Saylor
FDA

James Norman
FDA

Sherry Parker
SParker Consulting

Sam Albeke
Element Materials Technology

Ron Brown
Risk Science

Sandi Schaible
WuXi AppTec

Mike Ruberto
Material Needs

Christopher Houston
Bausch + Lomb

Ben Johnson
NSF International

Rebecca Bader
Cambridge Polymer Group

Eric Hill
Boston Analytical

Mike Eakins
Eakins & Assoc

Katie Grayson
Infinity Laboratories

Will Parker
Boston Analytical

Kevin Rowland
RQM Plus

Chongming Liu
SGS

Isaac Mohar
Gradient

With Comprehensive Coverage On:

- Data-Driven Assessment of E&L Derived from Manufacturing Equipment
- Improving the E&L GC/MS Workflow with Software Automation
- Panel Discussion: USP System Suitability Standard Proposal for Organic Extractables Testing, Published in USP PF 49(4)
- Managing AETs in Extractables Testing of Med Devices
- Preparing for ISO 10993-17: New Requirements and Tools
- Case Study and Regulatory Expectations in Chemical Characterization of Medical Devices per ISO 10993-18
- Reporting Analytical Data for Regulatory Submissions: Do's and Don'ts
- Medical Device E&L: Latest Activities of ISO/TC 194/WG 14
- Overcoming Challenges Associated with E&L Testing of Flexible Polymers
- E&L Assessments for Transdermal Patches
- Chemical Characterization in Biocompatibility for Med Devices
- Overcoming Common Analytical Challenges in E&L Studies
- Toxicology Assessment for E&L Studies
- Semiquantitative Sensitization Safety Assessment of Extractables and Leachables Associated with Parenteral Pharmaceutical Products
- The Biological Evaluation (and Regulatory Acceptance) of Design and/or Processing Changes to Commercialized Medical Devices
- And More!

With Representation From:

SGS TRIAD Cambridge Polymer Group Johnson & Johnson usp FDA janssen NSF Health Sciences

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ON drugDELIVERY

Thursday, November 2, 2023

7:00 *Registration Check-in & Complimentary Breakfast*

7:55

Chairperson Michael Eakins' Welcome & Opening Remarks

Regulatory Spotlight

8:00

Data-Driven Assessment of Extractables and Leachables Derived from Manufacturing Equipment

Dr. James J. Norman, Senior Pharmaceutical Quality Assessor FDA/CDER/OPQ/Office of Pharmaceutical Manufacturing Assessment

Extractables and leachables (E/L) derived from manufacturing equipment are a major component of FDA/CDER's evaluation of parenteral products. In the current state, E/L information is often not present or fragmented across multiple eCTD documents. This hinders development of data-driven assessments and leads to frequent information requests to applicants.

The aspiration we are working towards is building a structured E/L data set, calculating rapid risk scores, and retaining data to learn from and adapt our risk models. The first focus of the talk is a concise, example method for submitting structured E/L data. The talk will also cover initial internal research showing how structured data can save time and improve the consistency of E/L assessment.

8:25

Clearance of Extractables and Leachables Using Ultrafiltration and Diafiltration (UF/DF)—Preliminary Results and a Path Forward

Ping Wang, Director, Johnson & Johnson

Abstract Coming Soon

Complimentary WIFI brought to you by element

Technology Spotlight: Software Automation for E&L

9:05

Improving the E&L GC/MS Workflow with Software Automation

Benjamin Johnson, Manager, GC/VOC Lab, NSF International (Co-Authors: Don Kuehl & Yongdong Wang, Cerno Bioscience)

Due to the number of samples and the required replicates in each E&L study and the number of possible targeted and/or untargeted analytes typically detected in each sample run, it is highly desirable to have fully automated GC/MS analysis capable of operating in batch processing mode. While the analysis software that comes with most GC/MS instrumentation has built-in automated analysis capabilities, they all lack in some of the latest developments and emerging requirements in GC/MS analysis, namely, accurate mass and spectral accuracy available from even a quadrupole system, the full coverage and the automated application of the Retention Index (RI) in the latest NIST EI spectral library, improved deconvolution that tackles closely co-eluting peaks, and full integration with a given lab's existing or expanding workflow and the associated informatics system. In this presentation, we share our approach to these challenges.

A new software solution, GC/ID, has been developed to perform fully automated GC/MS identification and semi-quant including spectral library search (both forward and reverse), accurate mass and spectral accuracy analysis of molecular and fragment ions, RI calibration and confirmation including AutoRI even without RI standards, a new mixture search deconvolution (SMD) approach for closely co-eluting peaks, and the ability to highlight, adjust, and report the results.

GC/ID is a powerful off-the-shelf solution, but NSF, working with Cerno Bioscience, has been able to identify several customizations which will make the software more flexible and efficient. These include handling of internal standards, surrogates, custom compound classification, and identification of targeted vs untargeted compounds as well as additional quantification options. Additionally, work is being done to automate input and output files for interface with laboratory LIMS systems.

As part of the ANSI 61 certification program, NSF is committed to evaluating thousands of commercial products each year for both known and unknown contaminants. The identification and semi quantitation of these unknown compounds is critical as in many cases, their mere presence poses a health risk to the consumer. The Cerno GC/ID software was selected by NSF as a tool to help automate the more laborious aspects of this process, allowing faster and more thorough evaluations. The sophisticated deconvolution and library search functions produce high quality matches enabling the positive identification of compounds that would have previously only been identified by molecular weight and functional group(s).

9:45 **Case Study—Needles in a Pharmaceutical Haystack**

Christopher Houston, Senior Principal Scientist & Group Leader, Bausch + Lomb

CASE STUDY

Following the development of an ophthalmic solution, stability studies revealed unusual subvisible particulate matter with a needle-like crystal habit forming over time. The usual sources of undesirable subvisible particulate matter were quickly eliminated as root causes, leading to an extensive global investigation that ultimately resolved into a highly unusual example of a drug product leachable. As a case study, this presentation will focus on the investigation, its resolution, and lessons learned.

10.15 *Morning Coffee & Networking Break*

Spotlight onTransdermal Risk Assessment

10:55 **Extractables and Leachables Assessments for Transdermal Patches**

Michael A. Ruberto, Founder & Principal, Material Needs Consulting, LLC

Transdermal patches can be complex systems consisting of films constructed from various types of polymers. The pouches that are used to package and protect these patches often have a similar multilaminate construction that are bound together with tie layers or adhesives. The unique characteristics of transdermal patches can pose challenges when evaluating the leachables risk given all of the potential sources of leachables. Ensuring that the multilaminate pouches are compliant with USP <661.1> and <661.2> can also be an issue. The use of a transdermal patch is different compared to many other types of drug products and/or their delivery systems, since the transdermal patches are typically worn on the body for several hours or even days. They can see various temperatures conditions and even be worn during exercising where they can be extracted by sweat under elevated temperatures. Designing a leachables testing study plan that takes this type of an application into account is essential to meet FDA expectations. Handling change controls from vendors of the transdermal systems materials of construction also poses challenges. In general, the FDA expectations for an appropriate extractables and leachables risk assessment for transdermal patches can vary depending on the type of patch, its materials of construction, typical use, and packaging. They are considered to be higher risk drug products, but best practices for their testing have not yet been developed by the Product Quality Research Institute (PQRI). This presentation will focus on actual strategies that have proven to be successful in meeting the challenges described above for transdermal patches and their packaging systems.

11:35 **Advantages of Multidetector Systems for Semi-quantitative Accuracy in Extractables & Leachables**

Kevin Rowland, Director of R&D, RQM Plus

Abstract Coming Soon

12:15 *Complimentary Lunch, sponsored by*

Nitto Avecia Pharma Services

1:25 **Nitto Avecia Presentation**

Abstract coming soon

Regulatory Spotlight on Med Devices

1:50 **CHemical RISk Calculators (CHRIS): Regulatory Tools for Assessing Medical Device Leachables**

David Saylor, Materials Scientist, US FDA

Physics-based mass transport models are tools that can provide more clinically relevant exposure estimates for leachable substances in polymeric medical device components. However, there are inherent challenges with parameterization, validation, and implementation of these models and the level of regulatory acceptance can be uncertain. Therefore, we have developed the CHemical RISk calculators (CHRIS), which are a collection of web-based applications intended to facilitate the widespread use of these models in regulatory submissions. This presentation will cover the following topics:

* Mass transport models for exposure estimation

* Types of regulatory tools and hierarchy of regulatory acceptance

* CHemical RISk calculators (CHRIS) case study

* Next steps: tools for extractables testing

2:30 **Insights into Practical Issues Associated with Extractables Testing of Medical Devices**

Dennis Jenke, Founder & CSO, Triad Scientific Solutions

It is a well-known adage that "the devil is in the details." As authoritative texts associated with the chemical characterization of medical devices generally present concepts and generalities and lack granularity, sponsors seeking to design and implement extraction studies for medical devices occasionally struggle to establish critical experimental details that are scientifically sound, practical and regulatorily compliant.

This presentation provides insights into several of these critical experimental details, addressing concepts that include:

- The "It all comes out at Once" Paradox
- Exhaustive Extractions as a Source of Kinetic Release Data
- Predicting Exhaustive Extractions with a Minimum Number of Extraction Steps
- A Rational (?) Approach to Quantitation and Managing the AET
- What exactly is a "Semi-polar" Solvent?

Spotlight on Computational Modelling for E&L Analysis

3:10 **Recommendations for the Practical Use of Open-Source Computational Models to Predict the Genotoxic and Carcinogenic Potential of E&L Compounds**

Ron Brown, Risk Science Consortium, LLC

Computational models are often used to predict the genotoxic and carcinogenic potential of extractables and leachables in the absence of experimentally derived data. The ICH M7 and ISO/TS 21726 documents recommend the use of a statistically based model and an expert rule-based system to predict the genotoxicity and carcinogenicity of impurities in pharmaceuticals and extractables from medical device materials, respectively. Although commercially available software is often used for this purpose, there are a number of open-source programs that predict the genotoxic and carcinogenic potential of extractables and leachables with a high degree of accuracy. This talk will provide practical advice on how to use the open-source models to generate predictions of genotoxicity and carcinogenicity and how to interpret the model-derived results for the toxicological risk assessment of E&L compounds.

3:40 ***Afternoon Networking & Coffee Break***

Critical Issues Roundtable

4:00 **Modelling Biocompatibility for Devices: Toxicological and Chemistry Perspectives—A Roundtable Discussion**

Moderator: Michael Eakins, Eakins & Assoc.





Panelists:

- David Saylor, FDA
- Dennis Jenke, Triad Scientific Solutions
- Ron Brown, Risk Science Consortium
- Sherry Parker, SParker Consulting

Participants:

The Audience

5:00 ***Happy Hour Mixer***

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

Friday, November 3, 2023

7:00 ***Complimentary Breakfast***

Opening Panel Discussion—System Suitability Standards

8:00 **Discussion of Comments Received for the USP System Suitability Standard Proposal for Organic Extractables Testing, Published in USP PF 49(4)**

G. Prabhakar Reddy, Senior Principal Scientist–Team Leader, US Pharmacopeia
Moderator: Michael Eakins




Panelists:
G. Prabhakar Reddy, USP
Dennis Jenke, Expert Committee Member
Ping Wang, J&J

Discussants: The Audience

Implementing ISO 10993 Standards

8:40 **Lab X Said What Is in My Medical Device!?: Accurate Identification of Unknown Compounds from Non-Targeted Screening**

Dr. Rebecca Bader, Associate Director of Chromatography and Biocompatibility Specialist, Cambridge Polymer Group

Increased regulatory pressure with regards to 10993-18:2020 has driven laboratories to utilize increasingly conservative uncertainty factors that have resulted in lower analytical evaluation thresholds (AETs). Lower AETs have in turn increased the burden with regards to accurate identification of unknown compounds found during non-targeted screening. In some cases, the challenge of compound identification can lead to misidentifications that, at times, seem to defy logic and create unrealistic toxicological risk. When an unsuspected, potentially toxic substance has been identified in a medical device using GC-MS or LC-MS, a logical and defensible judgement regarding that compound identification is critical. Is the ID of the compound consistent with the ob-

served chromatographic behavior (retention time, peak shape, extraction solvent solubility)? For LC-MS, does the unknown respond primarily as a positive ion, a negative ion, or both, and are there significant adduct ions in the spectra? For a tentatively identified compound, do we also expect to detect this compound with another technique or an orthogonal detector? Even after these issues are considered, there may still be multiple ID possibilities consistent with those observations. The manufacturing materials and processes used to build the device should then be considered to make the most likely choice among the possibilities for an unknown compound. In this presentation, examples will be shown for GC-MS and LC-MS unknown identification using logic and experience for acceptance or rejection of tentative ID.

9:20 **Biological Risk Assessment in E&L Study Design**

Sandi Schaible, Senior Director of Analytical Chemistry & Toxicology, WuXi AppTec

Regulatory bodies are looking for objective evidence of safety. Designing your studies should take into account the biological risk assessment process (ISO 10993-1). This presentation will cover several key topics in this field, including:

- Importance of the Risk Assessment and overview of the process
- Key inputs for the Risk Assessment and how they relate to the E/L study
- Essential components of an E/L Study

10:00 **Preparing for ISO 10993-17: New Requirements and Tools**

Sherry Parker, President, SParker Toxicology Consulting, LLC

As the publishing of ISO 10993-17 is imminent, it will help to be prepared for the impact of the coming changes. The new revision is substantially changed from the last version, which is more than 20 years old. It has new requirements 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 guidance 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 new requirements, recommendations, and tools will be presented to facilitate the conduct of toxicological risk assessment of medical devices. While the scope of the changes seems overwhelming, this talk will demystify and provide practical solutions and tips for preparing toxicological risk assessments to comply with the upcoming standard, and use of new tools and approaches to handle the often massive amount of medical device extractables data.

10:30 ***Morning Networking & Coffee Break***

11:10 **Use of Toxicological Screen Limit (TSL) in Medical Device ISO 10993-17:2023 Risk Assessments**

Dr. Isaac Mohar, Principal Scientist/ Toxicologist, Gradient

Toxicological risk assessment (TRA) often accompanies extractable and leachable studies of medical devices and drug container closure systems. For medical devices, ISO 10993-17:2023 includes a Toxicological Screening Limit (TSL), which can greatly reduce the number of chemicals requiring a TRA. Extracted chemicals below the TSL can be concluded to not pose an appreciable harm to health without a TRA. Extracted chemicals above the TSL require a TRA that, depending on the device use, may necessitate derivation of short- and long-term tolerable intakes and consideration of multiple risk assessment scenarios. The use of the TSL has a number of caveats, which include requirements on extraction conditions and chemical identification. This talk will focus on the use of the TSL in medical device TRA with discussion of the analytical data needed to support this approach.

11:50 ***Complimentary Lunch***

1:00 **Analytical Considerations Surrounding Extractables and Leachables Testing of Drug-Delivery Devices**

Katie Grayson, Manager, Infinity Laboratories

Drug-delivery devices release a drug product over time into the human body. Depending on whether the product is intended to be submitted as a medical device or as a pharmaceutical drug product, the requirements for extractable and leachable (E&L) testing may differ. E&L testing for medical devices is typically defined as chemical characterization of medical device materials per ISO 10993-18. An E&L study for pharmaceutical drug products typically follows USP <1663> and <1664> for extractables and leachables asso¬ciated with pharmaceutical packaging/delivery systems.

This presentation will overview E&L studies, comparing and contrasting E&L requirements between pharmaceutical products and medical devices. Key elements re¬garding E&L study design of drug-delivery products will be discussed. Case studies on the E&L testing of drug-delivery products will be presented, including implantable infusion pumps and prefilled syringes.

1:40 **Overcoming Challenges Associated with E&L Testing of Flexible Plastic Formulations Used in Medical Devices & Pharmaceutical Manufacturing**

Sam Albeke, Chromatography Manager, Element Materials Technology

Flexible polymer formulations are instrumental for use as materials of construction in medical devices, single use components in manufacturer of drug substances and packaging of pharmaceuticals. However, performing extractable and leachable (E&L) studies on these flexible test articles can be challenging. E&L analysis of flexible plastics commonly leads to a higher number of extractables detected compared to rigid plastics due to the higher levels of additives and glass transition temperatures. There is an increased propensity for extractables to migrate from these softer plastics.

This presentation will focus on case studies which highlight some of these challenges from materials such as polyvinylchloride, polyurethane, ethylene-vinyl acetate, thermoplastic elastomers & fluorinated ethylene propylene with an emphasis on how the different plasticizers used can affect the extractable profile.

2:20 ***Afternoon Break***

2:30 **A Review of Leachables Method Development and Validation—Getting it Right the First Time**

Eric Hill, Senior Director of Chemistry Laboratories, Boston Analytical, & Will Parker, Director of Extractables & Leachables Laboratory, Boston Analytical

The final goal of any extractables and leachables program is the determination of leachables in product samples. This is typically achieved through analysis of product samples for leachables stored at both accelerated and shelf-life conditions. It is important that the methods employed for leachables analysis be appropriate to achieve this goal. A greater emphasis from regulators on method performance has been noted recently, with an eye on proper method validation. USP <1664> states plainly that "Validation of quantitative leachables methods should be accomplished according to industry accepted practices, criteria, and standards..." A focus of this presentation will be on the approach to leachables method validation, what is recommended or required in the industry, selecting appropriate method ranges, and discussion around treating leachables methods similar to impurities methods employed as part of quality control testing. Case studies will be presented to highlight these points, and inorganic leachables methods will be highlighted to show what ways they should be treated differently than their organic counterparts. The goal of this presentation is to survey the available recommendations and experience gained through real studies to promote better method validation, while keeping in mind the overall goals of a leachables study.

Critical Issues—A New Approach to Uncertainty Factors

3:10 **Practical Strategies to Decrease Uncertainty in Comprehensive E&L Analysis by LC/MS from an Industrial Perspective**

Chongming Liu, Supervisor—E&L Testing, SGS

E&L study plays a vital role in ensuring the safety and quality of drug products that come into contact with materials or containers. For the monitoring of potential E&L compounds with safety concerns, analytical evaluation threshold (AET) provides the conversion from dose-based threshold to concentration-based threshold during the analytical testing. Due to the variation of responses among different compounds during a screening study, there is an unneglectable factor (UF) for AET calculations in E&L studies.

This presentation will focus on the determination of lab-specific UF values and demonstrate a practical way from the industrial perspective to reduce the analytical uncertainty by an innovative simultaneous detection approach of orthogonal UV, MS, and a universal detector with less response variation – CAD (charged aerosol detector).

3:50 ***Close of Program***

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