PharmaED RESOURCES, Inc.

Extractables, Leachables, & Elemental Impurities 2018

Ensuring Quality, Safety, and Regulatory Compliance for Drugs & Biologics

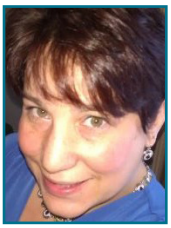
March 28–29, Racquet Club of Philadelphia, PA

Featuring Lessons Learned and Case Studies from Industry Experts:

Edwin Jao
Sr. Reviewer
FDA

Ping Wang
Sr. Manager
J&J

Dennis Jenke
Chief Executive
Triad



Bobbijo Redler
Principal Scientist
Merck

William Beierschmitt
Research Fellow
Pfizer

Ken Wong
Deputy Director
Sanofi Pasteur

And Comprehensive Coverage On:

- **Implementing USP <232> and <233> and ICH Q3D: Updates and Case Studies**
- **The Ongoing Development of USP Chapters <665> and <1665> Dealing with Materials and Components Used in Pharmaceutical Manufacturing Systems**
- **Injectables Drug Product Long Term Leachable Study Approaches and Regulatory Expectations – an Industry-wide Survey**
- **Case Study and Experience on Sanofi's implementation of BPOG's Leachable Risk Assessment Model**
- **Toxicology Issues in Extractables and Leachables**
- **Analytical Challenges in E/L Studies of Pre-Filled Syringes for Oil-Based Drug Formulations**
- **Extractables & Leachables Studies on Single-Use Components in Biomanufacturing**
- **Advanced Identification Methods for E/L from Packaging & Manufacturing Components**
- **Streamlining GC/MS and LC/MS Workflows for Extractables Profiling and Leachables Testing**
- **USP <661>, USP <661.1>/<661.2> : A Review of Compendia Based Polymer Extractable and Chemical Safety Assessment**
- **Use of Chemical Characterization and Risk Assessment of Medical Devices to Design Biocompatibility Testing Plans and Explain Test Results**
- **And Much More!**

With Representation From:

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Wednesday, March 28

7:45 *Registration & Complimentary Breakfast & Chairperson's Welcome*

Critical Issues – Updates & Case Studies on the Latest Compliance Implications of USP <232> and <233> and ICH Q3D Guidelines for Elemental Impurities

8:15 **ICH Q3D Compliance Strategy: Elemental Impurities Risk Assessment Documentation**

Timothy Shelbourn, Research Scientist, Eli Lilly and Co.

The final deliverable for an elemental impurities control/compliance strategy is the risk assessment document. While the scope of ICH Q3D and USP <232> is commercial drug product, an elemental impurities risk assessment for drug products in development is a recommended practice. This presentation will provide guidance for documentation of the EI risk assessment including where testing is required, where literature information can be applied and when it is appropriate to use a written assessment in lieu of analytical testing. A review of training modules and regulatory guidance documents with respect to the EI risk assessment documentation will also be conducted.

8:55 **Applications of ICP-MS in the Pharmaceutical Industry: The Path to Compliance with USP 232/233 and ICHQ3D**

Dr. Cristina Recasens, Analytical Chemist, Mass Spectrometry Group, Almac Sciences

Elemental impurities in finished drug products can originate from multiple sources during drug production and manufacturing, such as raw materials, excipients, catalysts used during drug synthesis, equipment and packaging. New directives to regulate inorganic impurities in pharmaceuticals and their ingredients are being described by the Guideline for Elemental Impurities ICH Q3D and the USP new General Chapters USP<232> (Limits) and <233> (Procedures) to replace the inadequate USP<231> (Heavy Metals). These directives will be implemented in 2018, and pharmaceutical companies must comply with these guidelines.

In this presentation, we will take a look at the different risk assessment approaches that can be used following the new guidelines and discuss different strategies to set internal specifications. Currently, many organisations do not have the resources or expertise to implement the new regulations within the set timeframe. Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) is the leading technology to satisfy both the limit requirements and the fast turnaround of samples. We will present the latest ICP-MS technologies used by Almac, their advantages for elemental analysis and the ICP-MS services that we provide. A case study on the development and validation of an ICP-MS method for the determination of elemental impurities, carried out in our laboratory, will be presented to show our approach for sample preparation, instrument parameters, and data analysis, interpretation and reporting.

9:30 **Determination of Metal Impurities— A Practical Approach from the Perspective of A Contract Laboratory**

Samina Hussain, Senior Chemist/ Metal Group Leader, Exova

There are several challenges a contract lab faces with the determination of elemental impurities in finished drug products, APIs, and excipients. Due to the expense and complexity of inductively coupled plasma instrumentation, a contract lab is often contacted by manufacturers to implement compliance with the new elemental impurities chapters, such as USP <232>, USP <233>, EP 5.20, and ICH Q3D. A common issue arising during the method development and validation process concerns setting appropriate specifications for a particular material. An evaluation of the specifications and how they relate to each and every drug product, raw material, and the manufacturing process as a whole is required. In addition, mastering sample preparation and analysis methods for a wide range of materials and specifications requires experience. An understanding of potential interferences associated with the instrumentation and specific analytical approach is essential. A risk-based approach to method validation will be presented.

10:05 *Coffee & Networking Break*

10:30 **ICH Q3D: Application to Legacy Products**

Jonathan Petersen, Senior Scientist, Merck

Abstract Forthcoming

E&L Risk Assessment— A Toxicological Perspective

10:55 **Toxicology Issues in Extractables and Leachables**

William P. Beierschmitt, Ph.D., D.A.B.T., F.A.T.S., Research Fellow, Drug Safety Research and Development, Pfizer, Inc.

An essential, critical component of the registration package for a parenteral product that is addressed by the toxicologist is the risk assessment of leachables and extractables. From a toxicology perspective, while extractable data can provide valuable information (i.e. what chemicals might migrate into the drug during storage), formal risk assessments are typically only performed on leachables (i.e. what chemicals did migrate into the drug during storage). The basic premise of this procedure is to assess the potential risk to humans resulting from unintentional exposure to the chemicals that migrate into drug product from packaging. For each

chemical, after determining the maximum potential dose a human might receive, the toxicologist uses available toxicology data, including experimentation if needed, to assess the potential risk. The route of administration and duration of potential exposure are just two of many factors taken into consideration when a risk assessment is performed. Overall, early involvement of the toxicologist in leachable and extractable studies from the earliest experimental planning stage through the data collection greatly facilitates arriving at a timely and successful assessment of these chemical impurities. Moreover, continued improvement in communication and information exchange with manufacturers regarding constituents/ chemical make up of packaging components would also facilitate the risk assessment process.

Regulatory Spotlight—Long-term Leachable Study Approaches & Regulatory Expectations

11:35 **Injectables Drug Product Long Term Leachable Study Approaches and Regulatory Expectations: An Industry-wide Survey**

Ping Wang, Senior Manager, Ph.D. Janssen R&D

Biologics Drug Product (injectables) long-term leachable studies are must-have in regulatory filings. However, there is no specific leachable study guidance and the study approaches vary from company to company. Inconsistent health authority inquiries also indicate that there is an urgent need for the industry to find a common ground, and have a unified voice to communicate with regulators.

As a 2018 initiative of ELSIE, an industry-wide survey will be conducted to understand the breadth and variety of the DP leachable study approaches. The survey will be focused on long term leachable studies of injectables in primary container closure systems. This interactive presentation will discuss the questionnaire and the goal of the survey. The final deliverable of this initiative (the survey results, and possible best practice recommendations) would help ELSIE members, pharma industry, and health authorities to ensure the leachable risks are properly evaluated.

12:05 *Complimentary Networking Lunch*

Regulatory Spotlight— An Agency Perspective

1:15 **Equipment Compatibility issues for Manufacturing of Liquid Dosage Forms— FDA/OPF's Perspective**

Dr. Edwin Jao, Senior Reviewer, FDA

Equipment compatibility is both GMP and review issues. General Expectations from OPQ Review and Inspection Team will be described. Currently available relevant regulation/Compendial/Guidance will be discussed. A risk-based approach will be proposed with illustrative case studies.

2:00 **Title Forthcoming**

Diane Paskiet, Director, Scientific Affairs, West Pharmaceutical Services

Abstract Forthcoming

Regulatory Spotlight—Implications of USP Chapter Revisions Pertaining to Pharmaceutical Manufacturing Systems

2:40 **The Ongoing Development of USP Chapters <665> and <1665> Dealing with Materials and Components Used in Pharmaceutical Manufacturing Systems**

Dennis Jenke, President, Triad Scientific Solutions

Polymeric components of drug product manufacturing systems will contact the manufacturing process stream, including process solutions, production intermediates, or the API, DS, or DP themselves, during manufacturing. During contact, process equipment-related leachables (PERLs) could leach from the component and accumulate in the process stream, potentially impacting a quality attribute of the process stream and affecting manufacturing process efficiency. If the PERLs persist through manufacturing, they could accumulate in the pharmaceutical product, potentially affecting product quality attributes such as stability and patient safety.

USP Chapter <665>, Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products addresses this situation via a risk-based approach for chemically characterizing polymeric materials and components used to manufacture pharmaceuticals/ biopharmaceuticals. USP chapter <1665>, Characterization of Polymeric Components and Systems used to Manufacture Pharmaceutical and Biopharmaceutical Drug Products) communicates the key concepts behind <665> and addresses the applicability and the application of <665>.

This presentation discusses the continuing evolution of <665> and <1665> as it makes its way through its third round of revision.

3:10 *Coffee & Networking Break*

3:35 **USP <661>, USP <661.1>/<661.2>: A Review of Compendia Based Polymer Extractable and Chemical Safety Assessment**

Allen Kesselring, Ph.D., Chief Science Officer, EKG Labs

While USP <661> has been a foundation point of product container safety, it has long been acknowledged to have several insufficiencies, particularly regarding the testing of final product containers. Due to these insufficiencies, the industry welcomed the concept of dividing Plastic (Raw) Materials of Construction (<661.1>) from

(Final) Plastic Packaging Systems (<661.2>). Unfortunately, as illustrated in the to be presented case study, even before formal implementation of USP <661.1> & <661.2>, it was discovered that certain gaps existed which would allow a material to easily pass USP <661.1>, but fail USP <661.2>. For these and other reasons, the "Packaging and Distribution Expert Committee" has put forth an accepted recommendation of the immediate reinstatement of <661> and a 3 year implementation of <661.1>/<661.2>. In addition to this case study and general commentary, several recommendations of <661.1>/<661.2> implementation will be presented along with discussion of industry impact of Chemical Safety Assessment expectations.

4:15 **Case Study and Experience on Sanofi's implementation of BPOG's Leachable Risk Assessment Model**

Ken Wong, Deputy Director, Sanofi Pasteur

Abstract Forthcoming

Q&A Forum

4:55 **Topic: Harmonizing Industry E&L Approaches and Regulatory Expectations**

Panelists:

- *Edwin Jao*, Senior Reviewer, FDA
- *Dennis Jenke*, President, Triad Scientific Solutions
- *Ken Wong*, Deputy Director, Sanofi Pasteur
- *Ping Wang*, Senior Manager, Ph.D. Janssen R&D

5:30 *End of Day One*

Thursday, March 29

7:45 *Complimentary Breakfast*

Research Spotlight—Considering Thermal Kinetics

8:15 **Thermal Acceleration of Leaching; Does Theory Match Reality?**

Dennis Jenke, President, Triad Scientific Solutions

Use of elevated temperature to accelerate extracting and leaching is commonly employed to decrease the duration of extraction and/or migrations studies. Various mathematical means are employed to establish and justify appropriate accelerating conditions of temperature and duration (time), including the use of Arrhenius-based kinetics. In this presentation, theoretical calculations are compared to reported leaching data to ascertain the degree to which theory meets practice, thereby establishing the applicability of the mathematical approaches.

8:55 **Extractables and Leachables Assessment for Cyrostore Cell and Gene Therapy Containers**

Raymond Colton, President, VR Analytical (Co-Authors: Sarah Brophy, Trent Volz, Ashley Boeckx, VR Analytical)

Cell and gene therapy products are primarily made in small-scale bioprocess systems using single use systems. Products are then stored frozen in bags until they are needed by the patient. A large body of work has studied how elevated temperatures affect extractable migration and thereby influence the extractables profiles of single-use systems. However, there is relatively little information available on how lowered temperatures may affect extractables profiles. This is particularly pertinent to the bio-container bags used for cryogenic storage of drug products in the growing field of regenerative medicine. To address this issue, polyolefin-based bio-container bags were filled with an aqueous solution containing 10% IPA, 10% DMSO, and 1% NaCl that was designed to approximate the extraction propensity of common cell solutions that might be cryogenically stored in a bio-container bag. The bags were stored at -80 °C for various time points and the extracts were analyzed by GC-MS/FID, headspace HS-GC-MS/FID, LC-UV-MS, and ICP-MS. The resulting data provide a unique insight into the effects of cold storage on the inorganic and organic extractables profiles of a bio-container bag.

9:35 *Coffee & Networking Break*

Critical Issues—Materials Characterization

10:00 **Implementation of a Material Based Approach for Managing the Risk of Leachables from Manufacturing Equipment**

Michael A. Ruberto, President, Material Needs Consulting

The characterization, qualification, and control of leachables from manufacturing equipment can be a daunting task for pharmaceutical companies. "Best practices" have been established by BPSA, BPOG, and USP <1665> / <665> for the initial evaluation of polymer based manufacturing equipment. However it is often unclear how this information can be effectively utilized for qualifying the individual components for use in the production of a particular drug product. This presentation will describe a practical, materials based approach that has worked in meeting the FDA's expectations for manufacturing equipment leachables risk assessments. Topics discussed will include:

- A proactive selection process for manufacturing equipment
- The role and utilization of vendor generated extractables testing
- A systematic testing plan for qualifying processing components for use in the manufacturing of multiple drug products using one set of simulation studies
- Examples of the strategic elements necessary for successful E&L risk assessment reports

10:40

Use of Chemical Characterization and Risk Assessment of Medical Devices to Design Biocompatibility Testing Plans and Explain Test Results

Steven Doherty, Associate Director, Analytical Chemistry, Toxikon

Recent regulatory guidance updates have highlighted the need to conduct material characterization as a critical step in the evaluation of the safety of medical devices. Initial comprehensive chemical characterization of devices can provide the basis to help guide necessary biocompatibility testing. The presence, or lack, of certain types of chemical compounds can support a rationale as to why some types of testing may, or may not, be necessary. Further, chemical characterization data can help to explain the results observed during biological testing. The data can provide context for the results and/or suggest means of mitigating the observed effect in a final product.

11:20

Application of the BPOG Standard Extraction Protocol to Multiple Component Types and the Lessons Learned

Bobbijo Redler, Principal Scientist, Merck

Abstract Forthcoming

12:00

Complimentary Networking Lunch

1:00

Successes and Ongoing Challenges with Implementation of Single Use Extractables Datasets

Chien-Ju (Cherry) Shih, PhD, Senior Scientist and James Hathcock, PhD, Sr. Director, Regulatory and Validation Consulting, Pall Life Sciences

Establishing consistent, high caliber expectations for component extractables data has been a major industry focus intended to streamline and accelerate the adoption of single use components. In this overview we will share lessons learned in execution of more than 17 studies using the BPOG protocol as well as limited studies using the USP <665> draft protocol. In addition, we review current challenges and potential solutions associated with compiling extractables datasets from multiple suppliers to perform comprehensive risk assessments on single use processes, as well as approaches to risk assess low to medium risk components for which detailed extractables studies are not available. The aim of this review of experiences to date is to drive further industry alignment among suppliers, end users and regulators that accelerates the adoption of single use technologies and serve the public good.

1:40

Advanced Identification Methods for Extractables and Leachables from Packaging and Components Used in Manufacturing Pharmaceuticals and the Effect of Analytical Methodology on the Number and Type of Compounds Identified

Mark Jordi, President, Jordi Labs

The process of Extractables and Leachables (E&L's) identification requires screening extracts for components of wide chemical diversity. E&L's have highly varied properties including widely ranging polarity, volatility and molecular weight. Identification of leachables in drug product matrices is made even more difficult by the fact that many drug products contain significant levels of background interferences. These interferences can suppress ionization in LCMS analysis or conceal signals from individual leachables. The FDA and USP have issued guidance and draft guidance on E&L analyses for products used in the manufacturing or packaging of pharmaceuticals. These documents provide recommendations regarding methods of identification but leave decisions as to the exact analytical methodology that should be applied to the sponsor. The types of analytical instrumentation and conditions used when conducting the E&L analyses affect the completeness and accuracy of E&L identification. In this presentation, we will demonstrate the effect of changes in sample work up prior to instrumental analysis on the number and type of E&L's identified from a pharmaceutical packaging material and a component used in the manufacturing of a pharmaceutical following guidance from USP 1663, 1664 and the draft guidance from USP 665. Parameters which will be examined include changes in surface area to solvent volume ratio and associated sample concentration, methods of solvent transfer procedures prior to GCMS and LCMS analysis such as liquid-liquid extraction, and storage conditions and age of extracts (extract stability). Variations in instrumental methods will also be examined including the use of traditional gas chromatography mass spectroscopy instrumentation versus more advanced systems such as Soft Ionization Quadrupole Time of Flight Mass Spectrometers. An advanced method of data reduction will be demonstrated comparing the use of differential analysis software to manual data-reduction. The presentation will then summarize the combined effect of changes in these parameters on the number and type of compounds detected and the accuracy of identification.

2:10

Streamlining GC/MS and LC/MS Workflows for Extractables Profiling and Leachables Testing

Smriti Khera, Strategic Marketing Manager, Agilent

When it comes to Extractables and Leachables (E&L) analysis, there are at least two critical analytical workflows involved, each with its own unique requirements. The first is extractables profiling which provides the first pass assessment and profiling of the worst-case

leachables that may be encountered in the final dosage form or manufacturing process. The second is the actual testing of the final drug product or bioprocessing/manufacturing steps for targeted leachables or to identify any new leachables that weren't previously expected. Both these workflows involve extensive use of LC/MS and GC/MS technologies to get a complete picture of volatile, semi-volatile and non-volatile organics in the extracts and samples. In this seminar, we will present how you can streamline your GC/MS and LC/MS workflows leading to overall laboratory efficiencies and the ability to gain greater insights from the analytical data you have collected.

2:50 *Coffee & Networking Break*

3:00 **Component Identification Beyond "EI Library search": USP <1663> in Practice**

Gyorgy Vas, Scientific Liaison, Intertek Pharmaceutical Services

Component identification is one of the most difficult, and in the meantime, one of the least discussed analytical activities related to extractable and leachable testing. Toxicological risk assessment requires reliable and highly confident component identification. Over the past couple of years, multiple studies were presented and discussed focusing on the extraction part of the data packages, and multiple case studies were presented with little or no focus on the component identification part. Many of the presentation indicated that it is an acceptable practice for volatile component identification to be completed using only the NIST based library search or using client developed proprietary library databases.

The introduction of high resolution accurate mass instrumentation (HRAM), hyphenated with GC-MS opens new possibilities beyond the unit resolution based identification workflow.

USP <1663> provides an excellent, practical, and science based approach for component identification, listing three level of identification (tentative, confident and confirmed).

This presentation will focus on case studies for the identification part of extractable-leachable testing, providing a state of the art workflow. Analytical data packages will be presented to compare unit resolution data vs. HRAM data sets.

3:40 **Analytical Challenges in Extractable and Leachable Studies of Pre-Filled Syringes (PFS) for an Oil-Based Drug Formulation**

Dujuan Lu, Ph.D. Technical Client Manager-E&L, SGS

Pre-filled syringes (PFS) are increasingly becoming a container of choice for storing and administering pharmaceutical products. PFS components and residues from processing tools may leach organic and inorganic chemicals into formulated drugs, as extractable and leachable compounds. As part of safety risk assessment, it is very important to identify and quantify those extractables and leachables as they may pose safety risks to patients and/or change the efficacy of the medical products.

This presentation will focus on a case study regarding the extractable and leachable testing of PFS for a drug formulation containing high content of castor oil. The choice of the extraction solvent systems and study design to bracket and mimic hydrophobicity and administration of oil based drug formulation will be discussed. In order to obtain a comprehensive extractable profile, multiple analytical techniques were used to identify and quantify the extractables, including Headspace (HS)-GC-MS/FID analysis for volatile organic compounds, GC-MS/FID analysis for semi-volatile organic compounds, LC-MS/UV analysis for non-volatile organic compounds, and ICP-OES analysis for trace elements. This presentation will show that internal database and High Resolution Accurate Mass (HRAM) data facilitate confident compound identification and unknown compound structure elucidation. Analytical challenges associated with the drug formulation containing high amount of castor oil during the leachable testing will also be discussed.

4:20 **Case Studies to Demonstrate the Susceptibility of Ophthalmic Drug Products to the Leachable Compounds Originated from Plastic Packaging Containers (Ex. LDPE)**

Ramarao Gollapalli, Manager, Analytical R&D, Akorn

It is well known that the polymeric compounds are widely used in packaging components of drug products. Therefore, the leaching behavior and permeability of these packaging components need to be well understood when used for pharmaceutical products. This is a critical part of the risk assessment in order to evaluate the safety and quality concerns of the finished product. Two ophthalmic product case studies will be presented to demonstrate how a product can be affected by the LDPE container directly or indirectly.

Case Study#1 will illustrate structural identification of an unknown impurity formed due to the reaction of an active ingredient in the drug product with the LDPE container. Case Study#2 will examine Migration of Diethyl Phthalate into the drug product from an extraneous source other than the original packaging system of the product.

5:00 *Close of Program*

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