PharmaED RESOURCES, Inc.

# Extractables, Leachables, & Elemental Impurities 2017—West Coast

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

**October 24–25, Sheraton La Jolla, CA**

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

- **A Discussion of USP Chapters <665> and <1665> Dealing with Materials and Components Used in Pharmaceutical Manufacturing Systems**
  - *Dennis Jenke, Triad Scientific Solutions*
- **Updates & Case Studies on the Latest Compliance Implications of USP <232> and <233> and ICH Q3D Risk Assessment Filing Guidelines for Elemental Impurities**
  - *Timothy Shelbourn, Research Scientist, Eli Lilly & Co.*
  - *Smriti Khera, Agilent Technologies*
  - *Diego Zurbriggen, West Pharmaceutical Services*
- **The Risk Assessment of Extractables—A Toxicological Window of Opportunity**
  - *William P. Beierschmitt, Research Fellow, Pfizer*
- **BPOG's Leachables Best Practice Guide: Study Design and Analytical Methods**
  - *Laszlo Litauski, Assoc. Director, Shire*
- **Challenges & Consequences for the Medical Device Industry by the Revision of Three Major ISO 10993-Standards**
  - *Dr. Albrecht Poth, Senior Toxicologist, Dr. Knoell Consult GmbH*

## *And Comprehensive Coverage On:*

- **Maximizing E/L Studies Through Aligning USP & ISO 10993 Requirements**
- **Leachable Risk Assessment of Dosing Devices for Parenteral Applications**
- **Extractables & Leachables Studies on Single-Use Components in Biomanufacturing**
- **Addressing Challenges with Polysorbate 80**
- **E&L Test Methodologies for Lyophilized Drug Products**
- **Industry Working Group Updates: PQRI & BPOG**
- **And Much More!!**

## *With Representation From:*

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## Tuesday, October 24

**7:30** *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*

**8:00**

### ICP-OES and ICP-MS Method Development and Validation for the Quantification of Elemental Impurities in Large and Small Molecule Drug Substances and Products

***Timothy Shelbourn, Research Scientist, Eli Lilly and Company***

Methodologies have been developed and validated for several small molecule and large molecule drug substances and drug products using ICP-OES and ICP-MS (with collision cell) for various elemental impurities. A variety of sample types and preparation schemes will be presented including direct organic solvent dissolution, aqueous dilution, and microwave digestion using nitric, hydrochloric and hydrofluoric acids. Elements and their associated toxicological limits were selected from USP <232> and ICH Q3D step 2b. The presentation will include some discussion of compliance strategy and the setting of internal specifications. Methods were validated per ICH Q2r2 and USP <233>. Acceptance criteria for accuracy, precision, linearity, and range were per USP <233>.

**8:30**

### USP<232> and <233> by ICP-MS and ICP-OES—Strategies for Eliminating Common Analytical Challenges and Example Cases Studies

***Jenny Nelson, Applications Scientist, Agilent; Smriti Khera, Pharma Segment Manager, Agilent***

Standards and regulations are established to ensure pharmaceutical products are tested to ensure they are safe and effective. As part of these testing requirements, USP<232> (Limits) and <233> (Procedures) calls for controlled experiments to verify that storage materials and conditions do not alter the elemental composition or toxicity profile of a drug.

In this presentation, we will take a look at the latest available ICP-OES and ICP-MS technologies and their relative benefits for elemental analysis. We will look at what technologies and strategies are most useful for addressing some commonly encountered analytical challenges such as effects of sample matrices, polyatomic interferences and false positives. Cutting-edge technologies such as ICP-QQQ will be discussed challenges such as dealing with higher than expected recoveries of 'challenging' elements such as Pb and As. We will also discuss 2 case studies on the elemental content of the plastic material of ophthalmic eye drop bottles and IV bags (a model for single use bioprocess system), using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) and Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) for the analyses. Data processing and evaluation was performed using Mass Profiler Professional (MPP) and Microsoft Excel.

**9:00**

### 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.

**9:30**

### The Changing Regulatory Environment Concerning Elemental Impurities and Container/Closure Systems

***Diego Zurbriggen, Supervisor, Leachables/Stability, West Pharmaceutical Services***

Elemental impurities in drug products can arise from multiple sources such as raw materials, excipients, manufacturing equipment and container closure/delivery systems. The Permitted Daily Exposure (PDE) and controls will pose challenges to the industry due to the multiple contributing sources and unique drug product requirements. Risk based approaches for elemental impurities are outlined in ICH Q3D and USP <232> and <233> and include specific elements to be consider from any source. Current specifications for extractable elements from elastomers and plastics are defined by USP and EP but these do not encompass all elements of concern. In addition the limits do not translate to drug product dosing, so the question remains on how elements of concern can be incorporated into a meaningful drug product risk assessment. The USP is the process of revising chapters for elastomers and addressing these issues. It has been noted that limits for elements will no longer exist, instead low levels of elements will be reported as found to be incorporated into a drug product risk assessment. This presentation will provide an overview of a risk-based approach for testing elastomeric closures for this topic. Extraction conditions, method parameters, and results will be discussed.

10:00 *Coffee & Networking Break*

## Panel Discussion

10:25 **Is the Industry Ready for the New Elemental Impurities Requirements?**

- Michael Eakins, Eakins & Associates
- Timothy Shelbourn, Eli Lilly & Co.
- Diego Zurbriggen, West Pharmaceutical Services
- Jenny Nelson, Applications Scientist, Agilent; Smriti Khera, Pharma Segment Manager, Agilent
- Dennis Jenke, Triad Scientific Solutions
- Samina Hussain, Exova

## E&L Risk Assessment—Toxicological Perspectives

10:55 **The Risk Assessment of Extractables—A Toxicological Window of Opportunity**

***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 matter for the toxicologist to consider during the development of a parenteral product is the risk assessment of extractables and leachables originating from components of the container closure system. While performing a comprehensive risk assessment on the leachables (i.e. the chemicals that actually do migrate into the drug during storage) is intuitive, assessing the safety profile of the extractables (i.e. the chemicals that might migrate into the drug during storage) can provide valuable information. Towards this end, a preliminary qualitative/quantitative risk assessment paradigm for extractables focusing on a subset of crucial endpoints (i.e. genetic toxicology, carcinogenicity, reproductive toxicology, irritation, and sensitization) will be described, including actual case studies where this methodology was employed. Since in the subsequent migration studies the impurities identified will typically be a subset of the extractables, assessing the latter for safety issues is a "window of opportunity" for the toxicologist to identify a potential safety concern prior to proceeding with the final leachable work.

## Regulatory Spotlight—Implications of Revisions to USP <665> & <1665>

11:35 **A Discussion 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>.

12:10 *Complimentary Networking Lunch*

## Regulatory Spotlight—Major Revisions to ISO 10993: Implications for the Industry

1:00 **Challenges And Consequences for the Medical Device Industry by the Revision to the Three Major ISO 10993-Standards**

***Dr. Albrecht Poth, Senior Toxicologist, Dr. Knoell Consult GmbH***

Three major standards, ISO 10993-1, -17 and -18 are going to be revised. The revision of ISO 10993-1 "Evaluation and testing within a risk management process" will include additional requirements to be evaluated and only the chemical characterisation will be mandatory, while all other toxicological endpoints will be evaluated within a toxicological risk assessment.

A major revision will be made on ISO 10993-18 to incorporate the technical and scientific experience developed during the last 10 years since its publication, including a more detailed description of experimental requirements for the investigation of extractables and leachables and a revision of the stepwise chemical characterisation process, including the setting of the analytical evaluation thresholds (AETs) in alignment with the TTC-concept.

A major revision of ISO 10993-17 on allowable limits for leachable substances is in works. Risk assessment approaches to use the concept of Threshold of Toxicological Concern (TTC), already established and accepted for genotoxic pharmaceutic impurities, are in discussion. If it can be shown that an impurity is below the TTC, then it is assumed that the chemical substance is of no significant risk. Based on the proposed revisions it can be foreseen that in future the chemical characterization will be a key parameter in the risk management process of medical devices.

1:40

## When NOT to Perform Extractable/Leachable (E/L) Analyses: A Risk Assessor's Perspective

***Kevin Connor, Ph.D., DABT***
***Technical Director, ToxSmart***

**As a tool in the safety assessment of biomedical devices, Toxicological Risk Assessment (TRA) has an increasingly important role in the chemical-based approach to safety assessment, which complements the more traditional approach, which is largely based on a combination of several in vitro and whole animal studies. New guidance even suggests that TRA might lead the way in the preclinical safety evaluations, being used to decide which biocompatibility studies are needed, and which are not.**

**TRA for medical devices based on an Extractable/Leachable (E/L) analysis is founded on the premise that if all constituents released from a device can be identified, then the safety of that device can be determined based on the toxicology of those constituents. The objective of the E/L analysis is to identify and quantify all substances that may be released from the test article during clinical use and is comprised of incubations of the test article in various media, e.g., water, ethanol, or hexane, at specific temperatures and durations. An obvious first point is that this doesn't hold up for every toxicological endpoint; thrombogenicity, for example, is not driven by the chemistry of a materials leachables. E/L data are of course relevant to most toxicological endpoints, but still, E/L analysis can face several pitfalls towards achieving the objectives of risk assessment, particularly if the analyst fails to consider the nature of device use and patient contact. Chief among the pitfalls is the assumption that the device will be immersed in a liquid medium as part of its clinical use, or during its storage. A device that only has limited contact with the skin for example, might be better evaluated with a wipe test, using artificial sweat as a transfer medium. Bioabsorbable materials will certainly have leachables that can be readily measured, but is leachability really the question? One of the greatest uncertainties currently plaguing the risk assessment of medical devices is in the use of data from a single extraction (24-72 hours) and the attendant assumption that the leaching of each analyte will continue for the duration of the exposure period. Many pitfalls in the E/L analysis can be avoided with proper study design. Lastly, the examples for why rote E/L analysis should be avoided will be discussed. For example, many implanted devices are sufficiently small to preclude levels of a leachable chemical from reaching a level of toxicological concern. It is incumbent on the risk assessor to complete a preliminary evaluation of the device before it is assumed that the E/L data will inform the safety evaluation. These and other potential pitfalls in the E/L analysis will be discussed together some success stories, where the E/L analysis has been used to streamline the overall safety evaluation of a device.**

2:20

## The Future of Drug Delivery Systems: Maximizing Extractable/Leachable Studies Through Aligning USP & ISO 10993 Material Safety Evaluation Requirements

***John Iannone, Director, Extractables, Leachables and Impurities, Amri Global***

**Industry & regulatory trends have demonstrated an increase in both, the needs and acceptance of utilizing chemical means to better understand material safety (suitability through biocompatibility & toxicology). Regulatory agencies value the use of chemistry as a way to increase visibility into material suitability, a critical component in developing combination products such as Drug Delivery Systems. Product developers have found this level of investigation to be paramount in risk mitigation and failure analysis. Both USP and ISO 10993 have had recent updates in proper guidance and continue to develop towards maximizing their utility in this activity.**

**As we look to the different approaches one can take to better understand the interaction between a material and its environment, it is advantageous to understand the concepts in both ISO 10993 and sections of the USP that relate to Chemical Characterization/Extractable & Leachable testing. Consideration of the benefits and limitations from these approaches currently outlined, and still to come, are critical in proper utility and ultimate success.**

**Guidance in analytical study design outlined in both the USP standards and ISO 10993 guidelines must be examined to determine those common elements with regards to suggested model solvents, extraction temperature and duration, analytical methods, and expectations for applying any resulting data towards safety assessments. It is just as critical to understand what the rationale is behind any differences between these regulatory recommendations. Ultimately, alignment between USP standards and ISO 10993 guidance is highly advantageous for reviewers & product developers. For certain combination products or cross over materials, such alignment is critical. It further eliminates unnecessary testing and helps to promote innovation and improved time to market, instead of stifling such advancements. As we increase the efficiency in bringing these solutions to market, we ensure these products are able to do what they were originally intended to do... improve patient care!**

3:00 ***Coffee & Networking Break***

3:15

## Potential Leachable Risk Assessment of Dosing Devices for Parenteral Application

***Ping Wang, Ph.D., Sr. Manager, Janssen R&D***

**Dosing devices (such as iv bags, iv admin sets, etc) are the last product contact materials before the drugs are administrated to the patients. The potential leachable risks are of high safety and regulatory concern. The dosing devices are usually made of various polymeric mate-**

rials, such as polyethylene, polypropylene, silicone, PVC, etc. Though it is impossible to test all dosing devices on the open market, some commonly used devices (20+) are tested for their potential leachables in this study. A generic biologics formulation is used to perform the in-use simulation. The leachables from these devices were measured using GC, HPLC, and ICP. The potential safety risk of these leachables from the dosing devices will be discussed.

4:00 **Extractables and Leachables Assessments for Lower Risk Dosage Forms**

***Michael A. Ruberto, Ph.D., Material Needs Consulting, LLC***

Most of the newly published "best practices" for extractables and leachables testing for container closure systems and manufacturing equipment are focused on high risk dosage forms, such as inhalation, injectable, and ophthalmic drug products. But what are the regulatory expectations for lower risk dosage forms such as oral and topical? The best practices state that a "risk-based approach" may be applicable and that "low risk doesn't mean no risk." Selecting materials of construction for the container closure systems and manufacturing equipment that are regulated for food contact applications according to 21 CFR 174-186 is a requirement; however, demonstrating the actual compliance with the appropriate type of food products is no longer a "check box" activity. Should the testing requirements be different for aqueous formulations compared to those having high concentrations of organic co-solvents? This presentation will focus on pro-active approaches for determining the leachables risk for primary and secondary packaging used with solid and liquid oral dosage forms as well as topical drug products. A step-by-step approach for interpreting and utilizing the indirect food additive regulations will be provided. Examples of performing assessments in the form of "paper exercises" versus E&L testing will be discussed. Case studies will include:

- Effectively assessing the leachables risk of bottles constructed from various types of polymers
- The impact of closures and corresponding liners and/or induction seals on leachables
- How to efficiently determine the leachables risk of adhesive labels
- E&L study plans for plastic and metal tubes used to package topical drug products

4:40 **Evaluation of E&L Test Methodologies for Lyophilized Drug Products**

***Ken Wong, Deputy Director, Sanofi Pasteur***

In the current USP <1664>, the powder for injection formulation risk associated with its interaction with packaging component were downgraded from Medium (listed in FDA 1999 guidance document for industry on container closure systems for packaging human drugs and biologics) to Low. A case study will be presented to examine the appropriate level of analytical test methodologies for an injectable lyophilized drug product with low likelihood of interaction with packaging component. Lesson learnt was implemented in future E&L study plan for lyophilized formulation with significant test cost savings.

5:30 ***End of Day One***

## Wednesday, October 25

7:45 ***Complimentary Breakfast***

### *Industry Working Group Update—PQRI Report*

8:00 **Points to Consider on Risks to Quality and Safety of Parenteral Drug Products from the Product Quality Research Instituted (PQRI) Leachables and Extractables Working Group**

***Diane Paskiet, Director, Scientific Affairs, West Pharmaceutical Services***

Studies for qualifying pharmaceutical containment and delivery systems should be guided by risks to patient safety and final product quality. The degree of testing required for the materials of construction, finished components, as well as complete packaging systems should be justified. Evaluations for extractables/leachables on PDP, ophthalmic drug products, large volume parenteral and biologics will have unique considerations. The chemistry of the materials individually and together with the final systems will provide the basis for understanding compatibility for various applications. This presentation will provide case examples related to compatibility of components and systems associated with aspects of safety and quality. Chemical characterization and simulation data acquired by the PQRI Leachables and Extractables Working Group will be referenced.

### *Research Spotlight—Extractables Studies on Polymers and Resins*

8:30 **Extractables Screening of Polypropylene Resins for the Identification of Suitability for Use Hazards**

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

Pharmaceutical products are packaged in containers so that they can be manufactured, distributed and used. Because extractables from such containers are precursors of leachable impurities in the product, extractables represent potential hazards to user safety.

Polypropylene resins are frequently used as materials of construction for packaging of liquid parenteral drug products. Thus extractables profiling of polypropylene resins may be an effective means of hazard identification associated with the resin's safe use.

Twenty-one PP resins were extracted using aqueous and organic extraction solvents and the resulting ex-

tracts were screened for extractables using appropriate general chemistry, chromatographic and spectroscopic methodologies. The resulting extractables profiles were toxicologically reviewed by a defined process to identify potential hazards given a specified therapeutic application involving chronic use of a large volume aqueous parenteral drug product (LVP).

The organic extractables profiles of individual PP resins were variable in terms of the individual extractable identified and their extracted levels, consistent with high variability in PP resin formulations and PP manufacturing. However, the profiles were similar in terms of the groups of extractable measured. Thus, for example, all the resins had extractables associated with antioxidants as all the resins contained antioxidants but the specific extractables for a given resin depended on the specific antioxidants present in that resin. Few of the targeted extractable elements were present in the extracts at measurable levels although most resins had measurable levels of extracted aluminum, silicon and alkali and alkaline earths.

A worst case extractables profile (all the extractables measured in individual resins at their highest levels) was toxicologically reviewed considering an aqueous large volume parenteral (LVP) drug product. This review established certain extractables as potential hazards whose actual toxicological safety risk assessment would require more rigorous data and a more rigorous process than those used for hazard identification.

9:10 **The Effect of Solvent Polarity Modifiers on the Extractables from HDPE, TPU, and PEBAX Resins**

***Roger Pearson, Ph.D., President Analytical Services, Aspen Research Corporation***

Extractables studies have become an integral part of product development in pharmaceutical products and also in medical devices. In the pharmaceutical arena extractables testing of container/closures is used to set the stage for leachables studies where leachables in the drug product is the measured endpoint for risk evaluation. In the medical device area the extractables information become the end product for risk evaluation as they are not normally analyzed for in the body. Guidance for medical device suggests sequential extractions of the device of interest until a compound of interest in the extraction solvent falls to 10% of it's initial extraction concentration. In the single use world, concentrations occurring over time and over different time periods have been considered.

In all cases, when designing extractable studies the questions always arise as to what solvent, what temperature and for what durations. This presentation will show findings from a study of extractables from resins of HDPE, TPU, and PEBAX. The study employed ethanol and isopropanol (IPA) as polarity modifiers and hexane as the most non polar solvent. Resins were extracted (2 grams per 10mL, ISO 10993-12) for 24 hour time periods at 50°C. Sequential extractions were decanted at the end of each 24 hour period and replaced with fresh solvent. One extraction was carried out without replacing the solvent for 7 days. Modifier concentrations used were 10%, 50%, 75%, 95% ethanol, 100% IPA and hexane. Extracts were analyzed by HPLC-DAD-TOFMS and selected extracts by GC/MS and ICP/MS. The study provides a unique data set to compare effects of modifier type (ethanol and IPA), modifier concentration (10%, 50%, 75%, and 100%), and extraction duration (1 day, 7day) on detected extractables and their concentrations from three widely used polymers.

9:50 ***Coffee & Networking Break***

## *Industry Working Group Update—BPOG's Risk Assessment Guidelines*

10:15 **SUS Leaching Propensity Assessment—A BPOG Guideline**

***Laszlo Litauszki, Ph.D., Associate Director, Engineering Systems Validation Lead, Shire***

A risk based quali cation approach requires a robust risk assessment methodology. The risk assessment must be science based, comprehensive, flexible and pragmatic. BPOG has developed a risk assessment guideline for the Biotechnology industry based on how Single Used Systems (SUS) are typically used. The guidance provides the framework and includes technical elements to be considered in assessing Leaching Propensity, i.e. the likelihood of unknown leachables entering the process stream and remaining in the Final Drug Product (FDP) at a concentration of concern. The guidance provides a level of flexibility and can be adjusted to individual companies risk mitigation practices while still keeping a comprehensive approach. The guideline is also intended to support regulators as a harmonized platform to assess the FDP Quality Risk originating from SUSs in Biopharmaceutical manufacturing, as it harmonizes the currently varying approaches into a uniform, structured model.

The model considers leaching kinetics and thermodynamics. A rating system is used to assess Leaching Propensity based on SUS material of construction and exposure conditions. The Leaching Propensity Assessment ranks the Single Use Systems and provides a scientific rationale when an Extractables & Leachables study is needed and where it may not provide added value. An example of the Leaching Propensity Assessment will be applied to a typical manufacturing process using SUS.

10:55 **Qualitative Assessment of Extractables from Single-Use Components Employed in the Storage or Manufacture of Biopharmaceuticals**

***Mark Jordi, President, Jordi Labs; Smriti Khera, Agilent Technologies***

Recent emphasis by the FDA as well as several high profile incidents have raised awareness as to the im-portance of the analysis of extractable and leachable compounds (E&L) from components employed in the storage or manufacture of biopharmaceuticals. The advent of single use bioprocess systems has introduced a new po-

tential source for E&L's as these systems are often comprised of polymeric materials. Several working groups (BPOG, BPSA), the FDA and USP have issued guidance on methodologies for performing E&L analyses for systems in contact with pharmaceuticals. These documents typically indicate that mass spectroscopy methods should be applied for discovery of E&L's but provide little guidance as to the exact process which should be applied. In this talk, we will present an example analysis on a single use bioprocess system and use this case study to demonstrate an LC/MS and GC/MS software workflow for analysis of E&L's. This workflow allows for the fast identification of E&L's as well as rapid comparisons between samples. A new high-resolution LC/ MS database consisting of over 1000 common E&L compounds and MS/MS spectra will be shown in order to quickly identify knowns from component extracts and perform early risk assessment using the references in the database. We will also describe differential analysis workflows for mining both LC/MS and GC/MS data and providing a convenient way of visualizing the large volume of data arising from these experiments and to facilitate presentation of results. Suggestions regarding method design with an emphasis on optimum standard selection will also be discussed.

## *Research Spotlight—Applications of USP & BPOG Protocols*

11:35

### Comparison of USP and BPOG Extractable Data for Autoclaved PES Filters

***Chien-Ju (Cherry) Shih, Ph.D. Senior Scientist, Regulatory and Validation Consulting, Pall Life Sciences***

A primary concern limiting the rapid adoption and implementation of single-use technology has centered on standardizing single use component data packages to be used for end-user risk assessments.

In this presentation, we will share experimental findings from the execution of two standardized extractable protocols proposed by the Biophorum Operations Group (BPOG) and the USP <665> panel on an autoclaved Polyether sulfone (PES) sterilizing grade filter.

Specically, filter capsules were extracted either in 6 suggested solvents for 30 min, 1 day and 7 days according to the BPOG protocol, or in solvents for 24 hrs per the USP protocol, with extract samples analyzed by headspace GC/MS, direct injection GC/MS, LC/UV/MS and ICP/MS.

The extractable results from GC/MS and LC/MS will be discussed in detail. Overall, the extractables observed in USP solvents (pH 3/salt, pH 10 buffer and 50% Ethanol) captured majority of extractable observed in other BPOG solvents (Water, 0.1M H3PO4, 0.5N NaOH, 5M NaCl and 1% PS80). Differences in 50% Ethanol and 1% PS80 pro les will also be shared, with the vast majority of compounds detected at the < 0.5 ppm level.

The experiences and lessons learned from this presentation are crucial to furthering the development of effective and practical standardized protocols for the use of single-use technologies. The aim is to help drive understanding and consensus approaches that serve the best interest of end-users, regulators, suppliers, and patients.

12:15 *Complimentary Networking Lunch*

1:00

### USP <661> and USP <661.1>/<661.2>— The Good, the Bad, the Ugly and the Future.

***Allen S. Kesselring, Ph.D., Chief Science Officer, E.K.G. Life Science Solutions***

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.

## *Research Spotlight—Applications of USP & BPOG Protocols, continued . . .*

1:25

### Investigation of pH and Ionic Strength of Extractables from Single Use Systems

***Raymond Colton, President, VR Analytical***

Both the USP and BPOG have recommended protocols for extractable testing for product contact materials including single use systems (SUS). There has been agreement about the ethanol/water and some conformance on the choice of low pH test media. The USP and BPOG are not in agreement about the choice of high pH test media and the merit of the other BPOG solvents, while not addressed by the USP, are still being debated. This paper presents data that shows the effect of ionic strength and pH on gamma irradiated filters, tubing/connector sets and bags.

2:05

### Evaluation of Single Use Manufacturing Components Using Different Extrication Media and Various Extraction Techniques: BPOG Vs. USP Approaches

***Gyorgy Vas, Scientific Liaison, Intertek Pharmaceutical Services***

Not only the packaging materials are contributing to the leachables; manufacturing equipment's can also be the source of contamination. Although the contact time is relatively short compared to the shelf life of the product, in contrary the temperature of the manufacturing can be elevated and some in-process conditions can be

more aggressive than usual storage conditions. Regulators recognized the issue associated with manufacturing equipment, and to meet with the regulatory expectations, regulatory guidance and USP chapters are being updated and implemented continuously. There are some extensive discussions and debates among scientist, how to provide meaningful analytical data, which support the safety evaluation of the manufacturing equipment, and the impact of the manufacturing related leachables to the final product. In one hand the BioPhorum Operations Group (BPOG), recommending to implement a very extensive extraction protocol using 6 different extraction media and a test period up to 70 days [BPOG paper]. Some of the media are very difficult to work with (5M NaCl; 1% PS-80) and analyzing the extracts with any instrumental techniques.

This presentation will focus to present case studies to evaluate single use systems (SUS), comparing the proposed BPOG and the USP methodology. Instrumental techniques are also evaluated as a part of the case study.

2:45 *Coffee & Networking Break*

3:10 **Extractables and Leachables: Challenges with Polysorbate 80**

***Michelle Kolodziejski, MS, Principal Chemist, Extractables & Leachables, Eurofins Lancaster Labs, (Contributing Authors: Thomas Lehman, Mai N. Jacques, Charles E. Ducker, Mathew S. Woods, and Andrew Blakinger)***

According to J.T. Baker, "Polysorbate 80 (PS 80) is a mixture of oleate esters of sorbitol and sorbitol anhydrides, predominantly consisting of the monoester, condensed with approximately 20 moles of ethylene oxide." PS80 is used to stabilize protein therapeutics in many pharmaceutical formulations including parenteral, ophthalmic, oral and topical preparations. Because PS80 is an integral part of the formulation for many pharmaceutical products it has become one of the most requested solvents for evaluating extractables profiles. As PS80 is a mixture of molecules of varying size, rather than a single uniform compound it presents many challenges for the laboratories that have to analyze it chromatographically and spectroscopically. In this presentation we will elucidate the complexities of PS80 and present data showing the mass spectral identification of the major breakdown products of the molecule, its accelerated degradation in glass when incubated at elevated temperatures for more than 7 days and its extraction power compared to other common extraction solvents.

3:50 **Potential Migration (Leachable) Safety Assessment of Label Materials for Drug Products in A Flexible Plastic Containers**

***Huaina Li Ph.D., DABT, Manager, Pharm. R&D, B. Braun Medical Inc.***

The Label Materials (such as adhesive, paper, ink, varnish, etc) are defined as "no direct contact" materials Per USP <1661>, which do not come into direct physical contact with drug products. However, depending on the container permeability and the label application process on the containers, the label materials can be considered as "potentially interacting" components. The requirements for extractables/leachables studies and safety/ toxicological evaluation per 21 CFR 210 and 211 are applying to label materials. The safety assessment should be specifically discussed in Modules for Toxicology Written Summary/Other Toxicity of the ANDA/NDA submission.

The approach for extractables/leachables studies as well as the toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

This presentation will discuss how to design the extractables/leachables studies, the evaluation of extractables/ leachables studies data, and conduct safety assessment for the Label Materials.

4:35 **Characterization of IV Bag for Extractables**

***Eric Hill, Director, Boston Analytical***

Polymeric materials used for pharmaceutical packaging must be thoroughly characterized and evaluated for their suitability of use. Prior to laboratory testing, a materials risk assessment that reviews the materials utilized in the test article, any vendor data available, the chemistry of the drug product, and the application of the component/ device/packaging is an invaluable first step in evaluating extractables and leachables. This exercise can identify leachables risk for all components in the container closure or manufacturing process, and prescribe appropriate testing to address these risks. A case study is presented for an extractables evaluation of an IV bag used to store aqueous solutions used for the treatment of blood plasma. This case study includes testing according to USP monograph <1663> and ISO 10993. A materials risk assessment was performed prior to any lab work, and a summary of these findings will be discussed. A materials characterization study with a controlled extraction study as well as a simulation study utilizing the solutions of use were performed. Procedures and equipment for the extract analysis will be included, as well as the analytical workflow for the identification of unknowns using Boston Analytical's extractables database. Extract analysis was completed utilizing Headspace GC-MS for volatiles, liquid injection GC-MS for semi-volatiles, LC-MS for non-volatiles, and ICP-MS for inorganics. Data for will be summarized for both the materials characterization and simulation studies. Final conclusions for the studies, including correlation between the extractables identified in each study will be presented.

5:20 *Close of Program*

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