Extractables, Leachables, & Elemental Impurities
Ensuring Quality, Safety, and Regulatory Compliance for Drugs & Biologics
September 14-15, 2015 Racquet Club of Philadelphia, PA

Featuring Lessons Learned and Case Studies from Industry Experts:

- Updates & Case Studies on the Latest Compliance Implications of USP <232> and <233> and ICH Guidelines for Elemental Impurities
  - Janeen Skutnik Wilkinson, Corporate Quality, Biogen Idec
  - Timothy Shelbourn, Research Scientist, Eli Lilly & Co.
  - Cindy Qin, Boehringer Ingelheim Pharmaceuticals

- Development and Justification of a Risk Evaluation Matrix to Guide Testing Necessary to Select and Qualify Plastic Components used in Production Systems for Pharmaceutical
  - Dennis Jenke, Baxter Distinguished Scientist, Baxter Healthcare; Chair, ELSIE

- Systematic Extractable Risk Assessment Of Polymeric Product Contact Materials In The Manufacturing And Packaging Of Biologics
  - Ping Wang, Principal Scientist, Janssen R&D, A Pharmaceutical Company of Johnson & Johnson

And Comprehensive Coverage On:

- Materials Characterization and Extractables and Leachables: Designing and Executing Studies
- Safety Assessment of Leachables
- Managing the Risks of Leachables from Single-Use Processing Equipment
- Extractables & Leachables Considerations in the Qualification and Validation of Single-Use Systems
- An Approach for E&L Evaluations of High Risk Infusion Devices
- Practical Approaches for Extractables/Leachables Study and Toxicological Assessment for Printing Inks for Large Volume Parenteral Drug Products
- Industry Working Group Updates from PQRI, BPOG, and BPSA

With Representation From:
### Monday, September 14, 2015

**7:30** Complimentary Breakfast & Chairperson's Welcome

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

**8:15** Elemental Impurities: Separating the Myths from the Facts: What you need to do now for Implementation  
*Janeen Skutnik Wilkinson, Corporate Quality, Biogen Idec*

With just over six months until Q3D becomes effective for new products and a little over a year before it goes into effect for existing products this presentation will sift through the myths vs the facts of implementation of ICH Q3D and the respective pharmacopoeial implementation strategies. Attendees will gain a better perspective on what needs to be done from a short term and long term perspective for compliance, and what key regulators are expecting. Finally, you will walk away with the most current and accurate news from one of the ICH Expert Working Group (EWG) and Implementation Working Group (IWG) members regarding the status of the IWG and next steps.

**8:45** Control and Monitoring Strategies for Elemental Impurities in Active Pharmaceutical Ingredients  
*C. Qin, A. Granger, H. Lee, M. Davis, R. Saraceno, Boehringer Ingelheim Pharmaceuticals Inc.*

Control and monitoring of elemental impurities in drug substance and drug product have become a hot topic recently due to the upcoming new USP 232, 233 and ICH Q3D guidelines. The pharmaceutical industry has been diligently working with regulatory authorities to generate practical strategies for global implementation of these elemental impurity guidelines. Although the new guidelines only apply to the final drug products, control and monitoring of elemental impurities in active pharmaceutical ingredients (drug substances) play a major role in ensuring compliance of final drug products with regulatory requirements. This presentation will discuss strategies and practices for control and monitoring of elemental impurities in active pharmaceutical ingredients, including risk assessment strategies, analytical method development/validation approaches and challenges, analytical measurement considerations, and documentation of risk assessment and associated analytical testing results. The investigation of out-of-specification and/or suspect results will also be discussed. The practices and strategies used for drug substances can be adopted for the final drug products and excipients.

**9:15** 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>.

**9:45** Coffee Break & Exhibit Viewing  
*Sponsored by NSF Health Science*

**10:10** Is the Industry Ready for the New Elemental Impurities Requirements?  
*Michael Eakins, Eakins & Associates  
Dennis Jenke, Baxter Healthcare Services; Chair, ELSIE  
Cindy Qin, Boehringer Ingelheim Pharmaceuticals Inc.  
Timothy Shelbourn, Eli Lilly & Co  
Janeen Skutnik Wilkinson, Biogen Idec*

**10:40** Safety Assessment of Leachables  
*Stephen A. Barat, Ph.D., Executive Director, Non-clinical and Translational Sciences Safety Assessment and Bioanalysis, Actavis, Inc*

Contemporary drug products make use of the advantages that modern container closure systems and materials provide for technical and functional purposes as well as marketing/brand recognition. Despite many advantages, these systems also present the potential for contributing impurities to the formulated drug product in the form of...
leachables. As with any impurity, since leachables do not provide any therapeutic benefit to the patient, their presence only makes for concerns for safety from inadvertent exposure. As such, the drug developer has an obligation to demonstrate the biological safety of any leachable substances when the drug product is used as intended. Approaches and considerations for conducting such safety assessments will be discussed.

- Introduce the issues encountered with leachables from drug/device combinations, container-closure systems and packaging.
- Discuss why the safety assessment of leachables is necessary.
- Outline appropriate approaches and various considerations necessary when conducting a safety assessment for leachables.
- Introduce the most current best practice for leachable safety assessment based on PQRI recommendations.

**Organic Impurity Profiling for Drug Products vs. (Screening) Leachable Studies--What Can We Learn?**

**John Iannone, Program Manager/Technical Specialist, Extractables/Leachables & Special Studies, Toxikon**

Organic Impurities are critical quality attributes of drug substances and drug products due to their potential to affect safety and efficacy. Organic Impurities in drug products can originate from many sources. The origin of an impurity may determine which guidelines/control limits to utilize in evaluating the impurity. Typically, an (Organic) Impurity profiling study is based on either 1) determining a suitable methods targeted to verify the presence of an expected impurity based on an evaluation of production processes, or 2) the utilization of a suitable API related technique, such as HPLC-UV, which is not always the best technique to verify the presence of organic impurities at trace levels. The targeted nature of the Organic Impurities profiling and typical methods utilized results in a probability that one may miss the presence of unexpected organic impurities at low concentrations.

Screening Leachable studies may assist in establishing a broad organic impurity profile for many drug products, with sufficiently low levels of detection.

The presentation will address 5 different case studies to show what could be learned from the raw data of a screening leachables study, when the drug product – which was in contact with the container closure system – would be interpreted as a “stand alone” test article, rather than in a comparative assessment with a blank drug product solution (not in contact with the C/C-system). Further, different types of drug products will be reviewed to examine the feasibility of this additional impurities profile approach.
Industry Working Group Update - PQRI

Industry Working Group Update: The Product Quality Research Institute (PQRI) Leachables and Extractables Considerations for Parenteral and Ophthalmic Drug Products (PODP)
Diane Paskiet, Director, Scientific Affairs, West Pharmaceutical Services

Recommendations on thresholds and best practices for identifying and qualifying leachables have been published by the PQRI Orally Inhaled and Nasal Drug Products (OINDP) Leachables and Extractables Working Group. This science-based approach is recognized as an effective way to reduce the level of uncertainty for leachables beginning in early stages of drug development. The methodology involves conducting controlled extraction studies to understand the chemistry of the materials in conjunction with a threshold to identify those potential leachables with safety concerns and this strategy is being proposed for PODP. While the safety concern threshold considers toxicological end points, attention to drug/biologic quality is also an important aspect for protecting the patient. Extractable data can be assessed for risk of material incompatibility with given pharmaceutical product that results in poor quality, however limits will be case by case. This presentation summarizes the current activities and findings of the Working Group along with considerations for assessing risks to pharmaceutical quality.

Systematic Extractable Risk Assessment Of Polymeric Product Contact Materials In The Manufacturing And Packaging Of Biologics
Ping Wang, Ph.D., Principal Scientist, Janssen R&D

In a typical biomanufacturing process, from cell culture to fill/finish, there are hundreds of pieces of polymeric product contact materials, such as bags, tubings, filters, connectors, O-rings, etc. The extractable risk assessment of those materials is important, and challenging. A strategic and systematic approach to evaluate the extractable risks across the manufacturing network will be discussed. The following factors will be considered: nature and location of the materials, in-use conditions, and availability of any relevant data. Risk-based approaches will be used to prioritize extractable testing when regulatory/safety concerns, budget, timeline, etc are all taken into consideration.

Materials Characterization and Extractables and Leachables: Designing and Executing Studies
Roger Pearson, Ph.D., President, Analytical Services, Aspen Research Corporation

With the upcoming changes to USP 661 the need for materials characterization and extractables and leachables studies will be more clearly defined. While the proposed changes provide guidance, the testing called for is by no means prescriptive and thus there still remains the need for designing the studies specific to the materials, systems or products in question. This presentation will review some of the best practices in the field and then present results of studies performed employing those practices. Cases will be discussed where the design went well and also where some hurdles had to be overcome. Studies involving single use bags, protective masks, devices and combination products will be presented.

End of Day One

Tuesday, September 15, 2015

Complimentary Breakfast

Morning Workshop

Industry Group Workshop – BPOG’s Extractable & Leachable Best Practice Protocol for Single-Use Components
Ken Wong, Deputy Director, Process Technology, Sanofi Pasteur
Dhaval Tapiawala, Technical Project Leader, Fujifilm Diosynth Biotechnologies
Kathryn McGohan, Associate Scientist II, Manufacturing Sciences & Technology, Bristol Myers Squibb
Seamus O’Connor, Associate Manager, Analytical Sciences, Regeneron
Gary Madsen, Senior Principal Scientist, Analytical R&D, Pfizer
Ping Wang, Principal Scientist, Janssen R&D, A Pharmaceutical Company of Johnson & Johnson

BPOG members will present BPOG’s standardized extractable protocol and provide details regarding its flexibilities for single-use components. The protocol will cover topics ranging from key reportable parameters, sample treatment, extraction set up, model solvents, time points, analytical test methods, and analytical test method integrity check. Followed by two proof of concept study data presentation for a bag and O-ring according to the BPOG’s extractable protocol.

Topics around leachable study and/or leachable stability study of single-use have not been widely presented or published. To better understand the practices among BPOG’s members, the leachable sub-team was formed to benchmark member practices and develop a best practice guide. For the first time, such a complete best practice guide will be presented covering the risk assessment process, leachable study design for various single-use
components and analytical considerations of the leachable test method(s) and validation. This workshop will cover:

- BPOG’s Extractable protocol for SUS and its flexibility - including myths and misconceptions
- BPOG’s Extractable protocol: Proof of concept study data (Seamus)
- BPOG’s Best Practice Guide for SUS Leachables Testing:
  a. Risk assessment - using a model standard approach;
  b. Leachable study design for Single-Use components;
  c. Leachable test method(s) – analytical considerations;
- Utility of BPOG’s recommendations – end user prospective

**10:15**

**Coffee Break & Exhibit Viewing**

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![IMPACT ANALYTICAL](image)

**10:40**


Janmeet Anant, Marketing Strategist, VR Analytical

Single-use systems (SUS) have found broad acceptance in pharmaceutical manufacturing based on their operational and economic benefits. To expedite selection and implementation of such systems, industry-wide discussions have been ongoing for several years with the goal of aligning basic qualification requirements. In particular, the development of consensus thinking on extractables testing for components and systems has been active for the past two years, along with the pursuit of a consensus standard for extraction and analytical methodologies.

Here we present a consensus position of the membership of the Bio-Process Systems Alliance (BPSA), the trade organization for the single-use industry based in Washington, DC. BPSA’s membership includes 48 corporate and institutional entities, among them component suppliers, systems integrators, end users, and independent testing laboratories.

**11:20**

**The Risk Assessment of Extractables—A Toxicological Window of Opportunity**


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.

**11:40**

**BPOG’s Best Practice Guide for SUS Leachables Testing**

- **a.** Risk assessment - using a model standard approach;
- **b.** Leachable study design for Single-Use components;
- **c.** Leachable test method(s) – analytical considerations;
- **d.** Utility of BPOG’s recommendations – end user prospective

**12:00**

**Complimentary Lunch**

**1:00**

**Proposal for the Standardization of Analytical Methods for Extractables Testing**

**Raymond Colton, President, VR Analytical**

Currently the USP, ASTM and ASME have committees working to establish test guidelines for extractables testing of product contact materials used during manufacturing, specifically Single Use Systems (SUS). The goal of the ASTM working group is to create a standard protocol for vendor-produced extractable data. One requirement of a standardized approach is dictating analytical methodology that will give consistent results regardless of the test laboratory, instrument vendor, analyst or test article. However, dictating requirements such as identifying all compounds above a specified signal to noise ratio will lead to a constant downward evolution of the reporting limits as instruments improve and more sophisticated software is employed for signal deconvolution and interpretation of the data. In many cases, the reporting limits are already sufficiently low so as to be inconsequential with respect to the risk to the patients. The other issue with increasingly low reporting limits based on signal to noise ratios is that at low reporting limits, the mass spectra are not sufficiently developed to allow for identification if the compounds if they are not already in the lab’s database. It is not expected that validated methods per ICH Q2(R1) will be required as extractable testing is considered a screening test. Yet, it is imperative that methods be qualified so there is reasonable confidence that any extractable could be detected if it were present at a reasonably low level. Therefore, instead of dictating specific instrument conditions and methods, a more sensible approach is to establish the goal of the analytical method (i.e., detect certain compounds at certain concentrations) and provide a means to determine whether a particular lab’s methods are sufficiently robust and sensitive. The specifics of the methods would be left to the lab to determine as along as the outcome was acc-
Practical Approaches for Extractables/Leachables Study and Toxicological Assessment for Printing Inks for Large Volume Parenteral Drug Products

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

Plastic Container Closure System (CCS) including directly label inks on Container surface are quickly becoming the primary choice of packaging system for large volume parenteral (LVP) drug products. However, there are challenges of designing extractables/leachables studies and safety assessment of container closure materials as well as printing inks for LVP products due to large volume dose up to 3-5 liters/day and the low level of leachables at ppb (ng/mL) to ppm (μg/mL). Currently, there are no universally accepted regulatory guidelines in place for extractables/leachables studies and assessing the risk of extractables/leachables (E/L) from printing inks.

This presentation will review the basics of printing techniques, composition and chemistry of ink systems, possible interactions of printing ink system with the packaging materials and the drug formulations. The presentation will discuss how to design printing ink extractables/leachables studies, the evaluation of extractables studies data and consequences to leachables studies, and how to conduct safety assessment particularly for label inks used for large volume of parenteral drug products through case studies.

Key takeaways:
- Considerations and approaches for printing inks extractables/leachables studies.
- How to design a reasonable E/L study (“to do enough but not too much”).
- How to conduct an actual toxicological evaluation of leachables.

Leachables from Unexpected Sources

Michael A. Ruberto, President
Material Needs Consulting, LLC

The subject of leachables from primary packaging and single-use processing equipment is not new and many companies have taken the appropriate measures to perform suitable extractables testing on these components to manage their leachables. However, there have been many reports in the literature over the past few years about leachables entering drugs from unexpected sources such as secondary packaging (including labels), bulk shipping containers, and pallets. Stresses from irradiation and warehousing could also induce leaching as well as other problems such as color and odor formation. These are the problems that result in unwanted media attention, prolonged investigations, and oftentimes product recalls. This presentation will discuss the leachables issues described above as well as provide some concrete measures that can be taken to reduce their risk, and allow pharmaceutical companies to have more control over their supply chain in addition to being better equipped to handle these incidents when they do occur. Some of the topics covered in this presentation will include:

- Proactive selection of materials that will be compatible with the drugs and protect them from external contaminants
- Identification of weak links in container closure systems that could be susceptible to leachables from secondary packaging and bulk shipping containers
- Forecasting of extractables and leachables
- Step-by-step approaches to identify the source of unexpected leachables

Case studies and examples will be utilized to illustrate each of these topics.

Coffee Break & Exhibit Viewing

An Approach for E&L Evaluations of High Risk Infusion Devices

Kurt Moyer, Ph.D.,
Director of Research,
NSF Health Sciences

High-Risk infusion devices, such as those for use in neo-natal and pediatric populations, represent a unique challenge when it comes to evaluating extractables and leachables. The experimental design is further complicated when the device is intended for intrathecal administration and implanted for an extended period of time. As opposed to simple drug-coated implantables, in which both drug and device compounds leach into the body, these low flowrate infusion devices serve as a conduit whereby the drug elutes through the device rather than off of it. In developing an extractables and leachables testing program for high-risk infusion devices, three primary actions must be considered: 1) leaching of device related compounds into the body, 2) leaching of device related compounds into the infusate and 3) leaching of drug-device compound adducts into the body. In addition, leachables from the device into the infusate may negatively impact the safety and/or efficacy of the drug itself.
Our study design, which was reviewed and agreed to by FDA, incorporates critical components of ISO 10993 and the PQRI recommendations, resulting in a hybrid approach that comprehensively evaluates the device. The implementation of this approach to the evaluation of a pediatric intrathecal infusion device will be presented as a case study.

**The Value of “Simulated Study” as a Tool to Predict Leachables in Prefilled Syringes**

Carsten Worsøe, Principal Scientist at Novo Nordisk A/S

The Product Quality Research Institute (PQRI) is currently developing recommendation and best practices for extractable and leachable documentation for Parenteral and Ophthalmic Drug Products (PODP’s). The recommendation describes the “simulated study” as a tool to predict actual leachables in the final PODP product. The presentation will describe the simulated study as the optimal study to predict actual leachables in prefilled syringes and how it can be used to reduce the risk for having critical leachables at a late drug development phase. The presentation will also describe how to perform the simulated study for prefilled syringes by two different methods and finally a number of cases will be presented showing the value of the simulated study.

- Relationship between extractables, simulated leachables and leachables
- What is the optimal tool/study to predict leachables in a prefilled syringe?
- How to perform a simulated study for a prefilled syringe
- Case studies on simulated studies in prefilled syringes

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