PharmaEd's

Extractables, Leachables, & Elemental Impurities 2014

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

March 24-25, 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**
  - *John Kauffman, Deputy Director, FDA*
  - *Timothy Shelbourn, Research Scientist, Eli Lilly & Co.*
  - *Janeen Skutnik-Wilkinson, Vice President, NSF Health Sciences, Pharma/Biotech*
  - *Samina Hussain, Senior Chemist/Metals Group Leader, Exova*
  - *Dennis Jenke, Baxter Distinguished Scientist, Baxter Healthcare Services; Chair, ELSIE*
- **Industry Working Group Update: The PQRI Leachables and Extractables Considerations for Parenteral and Ophthalmic Drug Products**
  - *Diane Paskiet, Associate Director, West Pharmaceutical Services; Team Member, PQRI E/L Working Group*
- **Analysis of Extractables & Leachables: Past, Present and Future Trends**
  - *Daniel L. Norwood, Distinguished Research Fellow, Boehringer Ingelheim*
- **Extractable Study Design and Data Evaluation of Polymeric Product Materials**
  - *Ping Wang, Principal Scientist, Janssen R&D, a Pharmaceutical Company of Johnson & Johnson*
- **Use of Simulation Studies to Support Change Control in Ophthalmic Packaging Systems**
  - *Christopher T. Houston, Senior Principal Scientist, Bausch+Lomb*

And Comprehensive Coverage On:

- **Safety Assessment of Leachables for Parenteral Drug Products**
- **Extractables & Leachables from Infusion Pump Systems**
- **Managing the Risks of Leachables from Single-Use Processing Equipment**
- **Extractables & Leachables Considerations in the Qualification and Validation of Single-Use Systems**
- **E/L Studies for Medical Devices Based on Blood Separation Technologies**
- **Simulation Studies During Pre-Filled Syringe Component Development**

With Representation From:

Lilly, ELSIE Extractables and Leachables Safety Information Exchange, MERCK, FDA, janssen Pharmaceutical Companies of Johnson & Johnson, NSF Health Sciences, Boehringer Ingelheim, Baxter, West By your side for a healthier world™, BD, B+L Bausch + Lomb, novo nordisk®, ASPEN Research, Forest Laboratories, Inc., Fresenius Kabi, Material Needs Consulting Medical Device and Packaging Services, Exova, TOXIKON Advancing Your Innovation

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Monday, March 24, 2014

8:00 *Registration & 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

8:45 **Elemental Impurities - Is Your Company Prepared for ICH Q3D?**
Janeen Skutnik-Wilkinson, Vice President, NSF Health Sciences, Pharma/Biotech

This presentation will cover the key elements of the ICH Q3D guideline, which is now at step 2. The participants will gain an understanding of what it means, what it does not mean and what their companies need to be doing now to prepare for implementation. ICH Q3D and the USP elemental impurities chapters <232> and <233> have generated a great deal of discussion and debate and this session will separate out fact from fiction.

9:15 **Total and Extractable Elemental Impurities In Plastic Materials and Systems: A Literature Review**
Dennis Jenke, Baxter Distinguished Scientist, Baxter Healthcare; Chair, ELSIE

Documents that address Elemental Impurities in marketed drug products are being developed by various organizations including ICH and USP. Although these documents make reference to packaging systems as a potential source of elemental impurities in drug products, they do not specifically enumerate how requirements for drug products translate to requirements for packaging systems. It is logical and appropriate, however, that requirements directed towards packaging take into account the existing literature on the topics of elemental impurities in and/or extracted from packaging, as it is expected that the requirements be science-based.
ELSIE, the Extractables and Leachables Safety Information Exchange, has reviewed the relevant literature concerning the elemental impurity levels in materials, primarily plastics, used in packaging. This presentation summarizes and discusses the results of that literature review, focusing specifically on:

- What elemental impurities are commonly found in packaging systems and/or their materials of construction, and
- What are the levels of these elemental impurities in, and extractable from, the packaging and their materials of construction?

9:45 **ICH Q3D Guideline for Metal Impurities**
John F. Kauffman, Deputy Director of the Division of Pharmaceutical Analysis, FDA

This presentation will provide an overview of the ICH Q3D Step 2b Guideline for Metal Impurities. It will begin with a brief synopsis of the background that led to the formation of the Q3D expert working group, and will emphasize the current state of harmonization between the entities that have prepared guidelines and standards for elemental impurities in pharmaceuticals. It will cover the scope of Q3D and will emphasize the risk-based approach to assessment and control of elemental impurities in pharmaceuticals, including consideration of container/closure systems. It will also describe the process developed to establish permitted daily exposures of elemental impurities in pharmaceuticals.

10:15 *Coffee Break & Exhibit Viewing*

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10:35 **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 L. Shelbourn, Research Scientist, Eli Lilly & Company; Expert Committee Member, USP

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>, EP 5.20, and draft 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>.

11:05 **Determination of Elemental Impurities – A Practical Approach from a Contract Lab**
Samina Hussain, Senior Chemist/Metals 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 manufac-

turers to implement compliance with the new elemental impurities chapters, such as USP <232>, USP <233>, EP 5.20, and ICH Q3D. Common issues include: setting appropriate specifications, mastering sample preparation, implementing appropriate contamination controls for ultra-trace analysis, and understanding of potential interferences associated with the instrumentation. These challenges will be discussed.

- Overview of ICP-MS
- Environmental Contaminants
- Common Instrument Challenges
- Method Development and Method Validation – Limit verses Quantitative
- Data – Employing Various Preparations

Panel Discussion

11:35 **Is the Industry Ready for the New Elemental Impurities Requirements?**
Michael Eakins, USP Expert Committee; Eakins & Associates
John Kauffman, FDA
Janeen Skutnik-Wilkinson, NSF Health Sciences
Samina Hussain, Exova
Timothy Shelbourn, Eli Lilly & Co; USP Expert Committee
Dennis Jenke, Baxter Healthcare Services; Chair, ELSIE

12:15 *Complimentary Lunch*

Extractables & Leachables – Regulatory Guidelines, Best Practices & Future Trends

1:30 **Extractables and Leachables in USP's Containers and Elastomeric Closures General Chapters**
Michael Eakins, Vice-Chair, USP Packaging, Storage and Distribution Expert Committee; Eakins & Associates

The presentation will address the USP's approach to extractables and leachables by providing an overview of its new draft General Information chapters on extractables <1663> and leachables <1664> and how these chapters relate to the packaging chapters <660> Containers - Glass, <661> Containers - Plastics and <381> Elastomeric Closures for Injections in the area of extractables. A proposed revision of Chapter <661> has been published in the Pharmacopeial Forum for comment and the proposed major changes will be briefly discussed. Many of the tests cited in the packaging chapters rely on spectroscopy. The USP has proposed a reorganization of General Chapter <851> Spectrophotometry and Light Scattering into a suite of General Chapters plus an accompanying suite of General Information Chapters. This proposal will be outlined.

2:00 **Analysis of Extractables and Leachables: Past, Present and Future Trends**
Daniel L. Norwood, Distinguished Research Fellow, Boehringer Ingelheim Pharmaceuticals

Over the past three decades the qualitative, quantitative and structural analysis of extractable and leachable organic compounds has relied on the hyphenated techniques and gas and liquid chromatography with mass spectrometry. These two analytical techniques continue to be the backbone of modern extractables and leachables analysis, which have tracked the significant advances in mass spectrometry over this time period. This presentation will discuss the current state of the art in extractables and leachables analysis, and describe future trends in the field.

- Understanding the history of extractables and leachables analysis
- The current state of the art in the E/L field
- Future trends in E/L analysis

3:15 *Coffee Break & Exhibit Viewing*

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Industry Working Group Update

3:05 **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 incompatibly 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.

E & L Considerations for Infusion Pump Systems

3:50 **Extractables & Leachables from Infusion Pump Systems**
Carsten Worsøe, Principal Scientist, Novo Nordisk A/S

Pump infusion systems are widely used with parenterals. This presentation will discuss how to deal with strategies for drug products that are administered with an infusion pump. Many different contact materials are used in infusion pumps and will be discussed here. Key takeaways from this presentation include:

- Characteristic contact materials and their related E&L's in infusion pump systems
- Regulatory expectations for E&L documentation for drug products used with infusion pump systems
- Which study is the appropriate E&L study – extractable, simulation or leachable study?
- How to correlate migration and pump flow relationship into an Analytical Evaluation Threshold (AET)
- Case studies with common leachables from infusion pump systems

4:35 **The Use of ISO 17025 Validated SOPs in Extractables Screening Studies**
Roger Pearson, Ph.D., V.P. Research and Development, Aspen Research Corporation

Much effort has been extended by numbers of groups in trying to standardize, at least to some extent, the protocols used in Extractables screening tests. Different solvents, extraction methods, times and temperatures are all variables of interest. However, no matter what extraction techniques are used, the final extracts need to be assessed by various analytical techniques. The results of those analyses are then used by risk professionals to guide the teams as to what detected compounds might be of concern if they are truly found to leach. Those assessments are based on chemical identity and estimated concentrations. Aspen has developed and validated four SOPs within its ISO 17025 accreditation scope that standardize the analyses by HS-GC/MS, direct inject GC/MS, ICP/OES, and anion IC. The process results in gaining an understanding of the confidence limits on estimated concentrations of unknown compounds in the extractables screening process. This allows a greater degree of confidence in setting the probable maximum concentration of a given compound without actually calibrating for that exact compound during the screening exercise. This can save a great amount of time and money.

5:15 *End of Day One*

Tuesday, March 25, 2014

8:00 *Complimentary Breakfast*

Risk Assessment for Single-Use Systems and Processing Equipment

8:30 **Recommendations for a Risk Assessment and Qualification Strategy for Single Use Technologies Used in the Manufacture of Biologic Drug Products with a Focus on Extractables and Leachables Studies**
Bobbijo V. Redler, Ph.D., Associate Principal Scientist, Merck

As the number of biotherapeutics in development continues to increase, so does the use of single use technologies (SUT) in the manufacturing processes. As a result, Biopharma companies are focusing more resources on the qualification of SUT in order to comply with current regulatory expectations and requirements. Risk management concepts can be applied biopharmaceutical development stages related to material quality such as material selection and compatibitliy and often include extractable and leachables evaluations as part of the qualification process. This presentation will provide a risk assessment model suitable for SUT used in biopharmaceutical manufacturing and demonstrate how the model is applied to identify additional studies, such as extractables and leachables evaluations, that are recommended to fully qualify a material for use.

9:10 **Managing the Risks of Leachables from Single-Use Processing Equipment**
Michael A. Ruberto, Material Needs Consulting, LLC

Polymers, such as plastic and elastomers, are quickly becoming the material of choice for the fabrication of single use processing equipment. These materials often contain stabilizers, colorants, fillers, and other specialty additives, making their formulation much more complex than metal or glass, and therefore, a greater risk for leachables. The issue that most pharmaceutical companies must address involves implementing a system to manage this risk. Performing a pro-active materials assessment for each plastic or rubber component in the production scheme can help to achieve this goal. This presentation will focus on the key questions to consider when selecting single-use equipment to ensure that it is safe and compatible with the drug. These questions take into account the chemical composition of the materials used to fabricate the components, the conditions of contact between the equipment and drug, as well as the solvating power of each ingredient used in the drug formulation. This type of evaluation will allow pharmaceutical companies to:

- Determine if vendor supplied extractables data is a "worst case" scenario
- Identify gaps and solutions to address these issues, including some additional testing if necessary
- Monitor supply chain integrity and handle vendor implemented material changes

A case study will be discussed that will provide a step-by-step approach for performing a materials assessment based on a thorough understanding of the polymers and additives used to construct the single-use equipment.

Spotlight on Simulation Studies for Extractables & Leachables

9:50 **Use of Simulation Studies to Support Change Control in Ophthalmic Packaging Systems**
Christopher T. Houston, Senior Principal Scientist, Bausch + Lomb

Many ophthalmic solutions and suspensions are packaged in semipermeable containers such that non-product contact components (labels, cartons, etc.) can influence the drug product leachable profile. As a result, supplier-initiated changes to these components must be evaluated carefully before implementation. Such evaluations can be complicated by short lead times and the use of affected components on multiple different products. Sometimes, a case for component equivalence may be made through the use of extraction studies. Often, however, extractable data are insufficient to draw an unambiguous conclusion. In these circumstances, simulation studies may provide the necessary data to reach a decision point in the evaluation of alternative components.

- Discussion on simulation study design for secondary packaging components and how these studies predict likely leachables.
- Simulation case studies and lessons learned.

10:30 *Coffee Break & Exhibit Viewing*

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10:50 **Simulated Studies During Prefillable Syringes Components Development**
Delphine Brissaud, R&D Senior Scientist, BD Medical

Prefillable syringes (PFSs) are widely utilized within the parenteral administration arena. A PFS is the packaging system of choice for small volume parenteral applications due to their capacity to reduce dosing errors and increase comfort upon drug delivery. PFS usually consist of a glass or plastic barrel, combined with an elastomeric plunger stopper and tip cap or needle shield, depending if a needle is attached or not.

Components in contact with the drug product will leach both inorganic and organic compounds into the drug product, however the delivered concentration based upon the drug application (dosages frequency and administration units) may render these leachables negligible with regards to safety concerns. However, in order to determine if the leachables can be consider as low risk, PFS and the drug product have to be assessed as an integrated combination product.

In order to anticipate mandatory leachables studies for registration purposes, which are under the responsibility of pharmaceutical companies; primary packaging component/system manufacturers are in a position to help by generating potential extractables lists usable for assessing compatibility with drug product. BD Medical Pharmaceutical Systems has developed a strong knowledge of PFS component materials and the direct link with the most sophisticated analytical characterization strategy and capabilities. Extractable studies are key in the initial material selection for PFS components. It is performed at the early stage of the component screening and then all along the primary packaging development process up to the final qualification when component design and manufacturing processes are frozen.

At this stage, simulated studies in selected media, adapted to the targeted drugs, under accelerated storage conditions are conducted. Such studies are expected to mimic and anticipate the outcome of leachables studies.

This approach, including simulated studies will be presented and illustrated by case studies:

- The development of a plastic prefillable syringe for pump applications: Sterifill Advance™.
- The development of the new generation of glass prefillable syringe BD Neopak™ designed for biotech drug applications.

11:30 **Extractable Study Design and Data Evaluation of Polymeric Product Contact Materials**
Ping Wang, Ph.D., Principal Scientist, Janssen R&D, A Pharmaceutical Company of Johnson & Johnson

Though polymeric materials have been widely used in the biomanufacturing process, the assessment of extractable profiles and leachable risks is still challenging, and varies from user to user. The extractables and leachables (E&L) are the major concerns from safety and quality perspective. The lack of relevant E&L data from suppliers presents end-users a great challenge. Strategies of developing relevant extractable study and

applying the data in the evaluation of safety concern threshold level will be discussed.

12:10 *Complimentary Lunch*

1:30 **Extractable and Leachable Studies for Medical Devices Based on Blood Separation Technologies**
Jianfeng Hong, Supervisor, Chemistry Laboratory, Fresenius Kabi, USA

A case study of extractable and leachable analyses of a tubular filter used in an automated plasmapheresis medical device is used to illustrate the extractable and leachable study practice at Fresenius Kabi. The study design, the determinations of concentration thresholds for extractable and leachable that require identification,and quantification, the analytical techniques and work flow used for extractable and leachable analyses will be presented.

Critical Issues—Safety Assessment, Qualification, and Validation for Parenteral and Single-Use Systems

2:10 **Safety Assessment of Leachables for Parenteral Drug Products**
Stephen Barat, Senior Director, Experimental Medicine and Science – Toxicology, Forest Research Institute

Leachable substances can emerge from various components of a container closure system and into the drug product, resulting in inadvertent exposure to the patient. As with any impurity, leachables do not present any therapeutic benefit to the patient. Therefore, their presence only presents a concern for safety. It is the responsibility and requirement of the Sponsor to demonstrate the biological safety of the leachable profile under the use conditions of the drug product. This session will introduce considerations necessary for leachable safety assessment and discuss current trends in approaching such matters during product development and life-cycle management. Key take-aways:

- Why safety assessment of leachables is necessary.
- Current trends in the safety assessment of leachables.
- How an actual toxicological evaluation of leachables is conducted.
- Working examples/case studies to illustrate the main points.

2:50 **Extractable and Leachable Considerations in the Qualification and Validation of Single-Use Systems**
Stephen Doherty, Ph.D, Director of Analytical Chemistry, Toxikon

In biomanufacturing, single use systems have provided many operational and economic advantages to the bioprocessing industry. From the adaptation of these polymeric platforms, the need for extractable and leachable qualification has become a significant aspect to validating the use of these SUS. This presentation will outline key considerations when modeling a single use system for determination of extractable & leachable profiles. Also, evaluation strategies and the thought process in designing appropriate analytical studies to assess these systems will be discussed. This presentation will benefit scientists and process engineers engaged in development, production, analytical characterization and approval of the utilization of Single Use Systems in bioprocessing and those who require a good working knowledge of extractables and leachables.

3:30 *Coffee Break & Exhibit Viewing*

Panel Discussion

3:45 **Framing the Current and Future State of Extractables & Leachables Analysis**
Michael Eakins, USP Expert Committee; Eakins & Associates
Daniel Norwood, Boehringer Ingelheim
Diane Paskiet, West Pharmaceutical Services
Michael Ruberto, Material Needs Consulting
Ping Wang, Jannsen R&D
Bobbijo Redler, Merck
Christopher Houston, Bausch + Lomb

4:30 *Close of Program*

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