Extractables & Leachables West Coast
Ensuring Quality, Safety, Suitability and Regulatory Compliance for Drugs, Biologics and Medical Devices
November 18–19, 2019, Sheraton, La Jolla, CA

Featuring Lessons Learned and Case Studies from Industry Experts:

With Comprehensive Coverage On:

• The Ongoing Development of USP Chapters <665> and <1665> Dealing with Materials and Components Used in Pharmaceutical Manufacturing Systems
• Issues Frequently Observed in Analytical Evaluation of Leachables in Drug Products (An FDA Review Experience)
• Toxicological Risk assessment of Medical Device Constituents—The New Working Draft of ISO 10993-17
• Understanding the Major Revisions to ISO 10993 and the New European Medical Device Regulations
• ISO 10993-18: Chemical Characterization of Medical Devices
• Application of ISO 109993-12 Exhaustive Extraction to Support Biocompatibility of Implantable Devices
• Exploring Biocompatibility vs. Chemical Assessment in E&L Study Design
• Revisiting the PQRI/USP Identification Categories for Leachables and Extractables
• The Use of Simulation Extractions to Address Leachables for Single Use Systems Extractable and Leachable Evaluation for Complex Pharmaceutical Formulations
• The Proper Use of Extractables Data – Aspects Beyond Extractables Measurement
• Advanced Identification Methods for E/L from Packaging & Manufacturing Components
• Understanding Leaching Associated with Lyophilized Drug Products Stored in Vial/Stopper Packaging Systems
• And Much More!

With Representation From:

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Monday, November 18

7:45

*Registration & Complimentary Breakfast & Chairperson’s Welcome*

### Regulatory Spotlight — E&L
**Expectations for Medical Devices & Drug Products**

Andrey Sarafanov, Ph.D., Chemist, Principal Investigator, Center for Biologics Evaluation & Research (CBER), FDA

This presentation provides overview of regulatory guidances and FDA requirements for assessment of leachables in new drug products and supplements to the approved licenses. Several cases representative for common deficiencies in study designs from the submissions are overviewed, and respective approaches to avoid such deficiencies are discussed.

**Issues Frequently Observed in Analytical Evaluation of Leachables in Drug Products (A Review Experience)**

Ron Brown, US FDA (retired), Risk Science Consortium, LLC

The biological safety evaluation of medical devices has typically involved the use of biocompatibility testing of an extract of the device or the device itself; however, an approach involving chemical characterization and risk assessment of compounds that are extracted or leached from the device is being increasingly accepted as a means to assess the safety of the device. Nevertheless, this approach can only be used with confidence to evaluate certain biological endpoints (e.g., systemic toxicity, carcinogenicity) and there is growing uncertainty about the use of the chemical characterization/risk assessment approach of E&L compounds as a standalone method for the biological evaluation of a device. This talk will outline the circumstances under which the US FDA will accept a chemical characterization/risk assessment approach as an alternative to biocompatibility testing of a medical device, will identify the situations in which the FDA may ask for characterization of E&L compounds to be done even if biocompatibility testing has been performed, and will explore the ways that the results of a chemical characterization/risk assessment of E&L compounds can be used in a biological risk management framework to evaluate the safety of a device.

### Exploring Biocompatibility vs. Chemical Assessment in E&L Study Design

Ron Brown, US FDA (retired), Risk Science Consortium, LLC

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### Coffee & Networking Break

8:15

8:55

**Exploring Biocompatibility vs. Chemical Assessment in E&L Study Design**

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### Revisiting the PQRI/USP Identification Categories for Leachables and Extractables

Daniel Norwood, Principal Consultant, Feinberg Norwood & Associates

In 2006, PQRI published the first comprehensive best practice recommendations for assessing extractables and leachables in drug products and their packaging systems. The essence of these recommendations was later incorporated into USP General Chapters <1663>, <1664>, and <1664.1>. Included in these best practices is an identification process for individual organic extractables/leachables, which includes mass spectrometry-based identification data elements and categories (e.g., tentative, confident, confirmed and unknown). This presentation will discuss the process used to develop the identification categories and examples available to PQRI prior to 2006. Additional examples developed since 2006 will be presented which challenge these categories. Modifications to the original identification categories will be presented for discussion. These modifications will likely be considered for incorporation into a revision of USP <1663>. This presentation, then, will highlight the following points:

- Discussing the process of developing identification categories
- Experience with implementing the original PQRI identification criteria and categories since 2006
- Examples which challenge the original identification categories
- What is the way forward?
The potential for product contact materials to leach impurities into drug formulations should be assessed with a risk-based approach. Higher risk applications may require specific testing to determine probable leachables. With final container closures, leachables evaluation usually targets specific known extractables using validated analytical methods with the actual drug product. When validating a method in the drug product it is often necessary to use sample prep techniques to remove analytical interferences. Therefore, it is not possible to know if other leachables have been removed by the sample preparation techniques which could lead to a false negative. USP <1664> allows for a simulation solution to be used in place of the drug formulation. This can be done to achieve analytical transparency so the potential leachables can be detected and identified. It can also allow the use of screening analytical methods as long as a subsequent toxicology evaluation does not show a safety risk. This can be the end-point for leachable evaluation for most product contact materials upstream of the final container/closure.

Minimizing Response Factor Variation for Extractables and Leachables to improve Quantitative Accuracy using Liquid Chromatography Mass Spectrometry (LCMS), Ultraviolet (UV) and Charged Aerosol (CAD) Detection

Kevin Rowland, Laboratory Manager, Jordi Labs

Chemical analysis for leachables is one of the the primary methods used to assess the risk to patients and consumers from substances which leach from pharmaceutical packaging, medical devices and food packaging. A number of high-profile incidents have demonstrated that leachables can have significant adverse effects on product safety and can also result in product recalls. The most widely publicized example of this is the migration of bisphenol A from baby bottles, but examples related to food contact applications (cereal packaging) and children’s medication have also been reported. The foundation of the chemical analysis and risk assessment process for Extractables and Leachables (E&L) is the accurate identification and quantification of species in the leachables solutions. Accurate identification and quantification of leachables is crucial if an appropriate toxicological evaluation is to be performed. Identification and quantification are both challenging areas of analytical science due to the wide variety of extractables and potential leachables, the complexity of many leachables solutions and the lack of suitable reference standards. The industry has approached this last problem, lack of reference standards, by using relative quantitation with surrogate standards which are predicted to show similar response. However, the magnitude of response factor variation, i.e. different detector responses for compounds present at the same concentration is unknown. In this presentation, we will report the results of a systematic study of the response factors for nearly 1500 E&L relevant compounds. Response factor variation was studied using three different detector systems (LCMS, UV, CAD) and the deviation in response factors by each detector was compared. These results were correlated with compound functionality in order to determine which detectors showed the least variation for different, but related, groups of compounds. A comparison of the stability of the response factors on multiple LCMS-UV-CAD systems was also performed to determine if response factor databases created on one instrument platform can be migrated to other platforms without creating additional error. The overall effect of response factor variation on quantitative accuracy will be highlighted and recommendations will be given for the optimum detector configurations to minimize quantitative error.

Understanding Leaching Associated with Lyophilized Drug Products Stored in Vial/Stopper Packaging Systems

Steven Zdravkovic, Senior Research Scientist, PPD

Drug products stored as a solid lyophilized cake or powder are becoming common in the pharmaceutical industry due to the increased development of biologic products, which are often unstable in solution. As with any drug product, the quality of a lyophilized product may be negatively impacted by substances leached from its primary packaging system; typically a glass vial and butyl rubber stopper. However, contrary to expectations, it has been observed that lyophilized formulations have an increased propensity to leach substances from their primary packaging system as compared to a liquid formulation when all other factors are equal. The goal of this presentation is to provide insight into the leachable
profiles associated with lyophilized products, estimate the extraction power of a lyophilized product relative to other solid and liquid media, and determine the extent of patient exposure to these leachables after reconstitution, storage, and administration of the lyophilized drug product via polymeric storage/delivery systems.

Extractables and Leachables Assessments for Transdermal Patches

Michael A. Ruberto, Material Needs Consulting, LLC

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

4:40 Extractables & Leachables Case Study for Transdermal Patch Product

Eric J. Hill, Boston Analytical (co-authors: Steven J. Martin, Christopher M. Weikert, SiO2 Medical Products)

Transdermal patches are used to incorporate the active ingredient of the drug into the circulatory system through the skin. Transdermal products are gaining popularity in the industry due to their ease of use, however they present unique leachables concerns compared to traditional drug products. Transdermal products incorporate a backing layer, release liner and storage pouch that all can serve as sources of leachables to the patient during the administration of the transdermal patch. The U.S. Food and Drug Administration (FDA) Guidance for industry has categorized transdermal patches as a packaging type with a high concern associated with the route of administration. The FDA has specifically requested leachables studies be performed for transdermal patch products, which include methodologies that mimic skin-contact during typical usage including exercise conditions. Design of suitable leachables studies that mimic “in-use” conditions is very challenging. Herein, we propose a skin-contact simulation study based on the single-side extraction to mimic the skin-contact under conditions of exercise in the worst-case clinical usage. In this study, a special customized extraction vessel is applied to perform the single-side extraction without extracting the backing layer. A sweat simulation solvent is used to mimic the extracting power of sweat under conditions of exercise. The resulting extracts were analyzed as appropriate for volatiles, semi-volatiles, non-volatiles, and metals with gas chromatography/mass spectrometry (GC-MS), liquid chromatography/mass spectrometry (LC-MS) and inductively coupled plasma mass spectrometry (ICP-MS) to provide comprehensive leachables profiles. These data were used to develop target compounds for a subsequent leachables study. Example data and the study outline will be presented.

5:20 Close of Day One.

Tuesday, November 19

7:45 Complimentary Breakfast

Critical Issues—Exploring the Major Revisions to ISO 10993-1, -17, & -18: Methodological & Toxicological Considerations

Stephen Doherty, Ph.D., Assoc. Director, Analytical Chemistry, Toxikon

The update of ISO 10993-1 was released in August 2018. This update included several new concepts as well as some reinforcement of previous guidance. Notably is the revision of the Biocompatibility Evaluation Endpoint charts with the additional of physical/chemical characterization. This change signifies the importance of the chemical characterization of the device as part of the overall assessment. Perhaps more important is the need to utilize a risk-based strategy for planning and conducting testing for support of regulatory submission. In this presentation, we will review some of the changes in the document and the role chemical characterization can play in fulfilling the requirements of 10993 both in initial submission support and throughout the life cycle of a medical device.
8:55 | ISO 10993-18: Chemical Characterization of Medical Devices

*Ted Heise, Vice President, Regulatory & Clinical Services, MED Institute*

The presentation will provide an overview of the approach to chemical characterization, describe changes in expectations that are developing with revision to the standard currently underway, and illustrate lessons learned from a brief case study.

9:35 | Networking Coffee Break & Exhibit Viewing

10:00 | Toxicological Risk Assessment of Medical Device Constituents: The New Working Draft of ISO 10993-17

*Sherry Parker, Senior Director of Regulatory Toxicology, WuXi AppTec*

ISO 10993-17, which was last revised in 2002, has undergone a significant revision and is now in the Working Draft Stage. The proposed title is “Toxicological Risk Assessment of Medical Device Constituents,” and revised standard will expand from current guidance on establishing allowable limits of leachable substances, to conducting a toxicological risk assessment of medical device constituents. Topics to be addressed will include hazard identification, exposure assessment, dose-response assessment, and risk characterization. There will be emphasis on the use of expert judgement to determine whether the toxicological risks of exposure to extractable or leachable chemicals in medical devices are acceptable, and what additional steps may be taken to mitigate risk.

10:40 | Q&A: Ask the Experts

11:10 | Case Study: Application of ISO 10993-12 Exhaustive Extraction to Support Biocompatibility of Implantable Devices

*Bobbijo Redler, Principal Scientist, Merck*

Abstract Coming Soon

11:50 | Complimentary Networking Lunch

1:00 | Challenging Analytical Methods on the Bench with Real Client Samples to Improve Extractables & Leachables Data—a Critical Bridge Towards Product-Patient Safety

*Samuel N. Kikandi, PhD., Manager, Sr. Scientist Extractables and Leachables Study Executions Lead, Manufacturing Technology, Sanofi*

Biopharmaceutical industries are increasingly using Single-Use Systems (SUS) as bioreactors, product pathways, storage and packing drug products. Because of that, SUS are reducing manufacturing costs and improving productivity, but on the hand, posing product patient safety risk due to potential contamination with extractables & leachables (E&L) from SUS. Because of that concern, it has become a huge challenge for biopharmaceutical companies to qualify product contact materials (PCM) and maintain compliance to Health Authorities (HA) submission requirements. A key factor in PCM qualification is the quality of analytical methods utilized in testing for the potential E&L species. Testing for these species could utilize analytical screening methods whose performance has not been evaluated in client’s real product matrix. Failure to do is likely to increase the chances of method implementation errors that could eventually expose patients to contaminated drug product.

This presentation will highlight the typical E&L qualification steps, checklist but more importantly, case studies of in-house analytical methods that demonstrated high quality performance in multiple real drug product samples. Further, the presentation will show one of the test methods that was not only used to check the performance in various sample matrices but also used to address business critical non-conformance situation.

1:35 | How Far Have We Come and What Are the Limits of Identification in E&L Studies

*Roberto Menzel, Laboratory Supervisor Extractables & Leachables, Sartorius-Stedim Biotech GmbH*

Extractables studies of Single-Use (SU) equipment used in biopharmaceutical manufacturing are performed almost since decades and a tremendous pool of knowledge was published. Contrary to that, an Extractable laboratory report can contain wrongly identified common additives and even a significant level of unknowns. The result of the toxicological evaluation of such inadequate data can lead to an exclusion of SU components especially in critical applications such as the manufacturing of large volume parenterals. This contribution will illustrate the existing key knowledge and will show that the level of unknowns can be remarkably low in E&L studies if general chemical and physical basics are applied in data interpretation. A case is presented were material knowledge and a literature review helped to identify most previous unknowns.
Adapting to Standardization of Extractables Testing in the Single-Use Industry

Laura Moody, Product Manager for Single-Use Systems, Bosch Packaging Technology

As integral contributors within the pharmaceutical supply chain, single-use component suppliers are required to provide extractables data for their products. However, a lack of standardization with regard to extractables testing and reporting has placed a cumbersome burden on pharmaceutical manufacturers to interpret and report applicable data to the regulatory agencies. The publication of BPOG’s standardized extractables testing protocol as well as the draft chapter USP <665> has provided guidance for single-use technology end users and suppliers alike. In response to a greater adoption of this standardization as a requirement by pharmaceutical manufacturers, the presentation will discuss how single-use component manufacturers have been expanding their legacy extractables testing to encompass the broader scope of solvents and time points included in the standardized protocols.

Reactive Leachables with Insulin and Biopharmaceuticals: Combined In-Silico Model with Experimental (Analytical) verification of Proof of Concept, using INSULIN as a Marker Compound

Matthew R Jorgensen, PhD, Senior Extractables and Leachables Expert, Nelson Labs

In the EPREX case, leachable induced immuno-responses caused severe adverse reactions to CKD patients. Although the EPREX case is often referred to by the E/L community to stress the importance of an in-depth E/L evaluation of the C/C-system, it also showed that the traditional E/L approach for container/closure systems may not always be adequate in predicting leachables could chemically modify proteins, potentially causing immunogenicity through the formation of “anti-drug-antibodies”.

The FDA Guidance for Industry: “Immunogenicity Assessment for Therapeutic Proteins” (2014) describes anaphylaxis, cytokine release syndrome, infusion reactions, non-acute reactions and cross-reactivity to endogeneous proteins as the associated safety concerns when considering immunogenicity as a result of chemical interaction between leachables and proteins.

The presentation will address 2 ways of predicting if any of the chemical compounds, found in the extraction profile of container/closure component, could lead to a chemical interaction if any of those extractables would become a leachable: (1) how to perform an in-silico reactivity approach of a very broad set of commonly known extractable compounds and (2) a chemical reactivity test to actually screen for residual chemical reactivity.

In addition, a chemical reaction model, based on Insulin as a marker compound was developed to actually verify the in-silico predicted chemical reactivity and compare the outcome of the in-silico exercise with the observed reactivity between a predefined set of extractables and insulin.

Coffee & Networking Break

Extractable and Leachable Evaluation for Complex Pharmaceutical Formulations (Organic Emulsions, And Polymer-Based Formulations)—Testing of Manufacturing Surfaces Through Packaging: How to Deal Outside the “Normal Range” of the USP Standard

Gyorgy Vas, Scientific Liaison, Intertek Pharmaceutical Services

Evaluation of manufacturing systems and the product related packaging is a complex analytical task. To execute the testing, USP standards must be followed when they are available, however even when standards are available they may not be appropriate to follow, since the formulation complexity is not addressed in the standard. The intention behind any standard is to cover 85–90% of the applications, and therefore a small percentage of the applications can fall outside the “normal range.”

USP <665> provides an excellent framework for evaluation of polymer-based manufacturing systems, for the majority of the systems, however it has some gaps for highly complex organic based formulations. This presentation will focus on presenting a case study related to a highly organic (80% organics) based process flow evaluation for extractables and leachables. A step by step approach will be presented for the evaluation, including various extraction and detection techniques. For proper evaluation state of the art sample preparation and HRAM based GC-MS and LC-MS detection systems were used.

A Case Study to Investigate Fragmentation Mechanism of a Leachable from Secondary Packaging

Dujuan Lu, Ph.D. Manager/Global Lead-E&L, SGS(Co-authors: Chongming Liu, Danny Hower, Xiaoteng Gong)

Primary packaging components are those that are either in direct contact with the drug product or have the potential to be in direct contact. The common primary packaging includes vial, bottle, tube, syringe, and bag. These components may also include container liners and closures such as caps, stoppers and metering valves. Secondary packaging components are integral to the final marketed package but are not in direct contact with the drug product, such as pouches, labels, and cartons. Although this indirect contact decreases the possibility of migration, there is still a risk for leachables. Leach-
ables derived from secondary packaging components are typically more volatile than those arising from primary packaging.

This presentation will focus on a case study on fragmentation mechanism of a cyclic ester, which was found as a leachable from secondary packaging. During the GC-HRMS/FID analysis for volatile and semi-volatile organic compounds, the compound was originally shown as an unknown. By using the High Resolution Accurate Mass (HRAM) in both Electron Ionization (EI) and Chemical Ionization (CI) Modes, we were able to obtain the molecular ion information and chemical composition of this compound. Tandem mass spectrometric experiments by GC-MS/MS were also performed to obtain fragmentation information at different collision energies. We were able to successfully identify the unknown compound and have demonstrated that the current literature shows incorrect information on one of the major fragment ions. This presentation will show the importance of extractable studies on secondary packaging and that High Resolution Accurate Mass (HRAM) data can facilitate confident compound identification and unknown compound structure elucidation.

Available extractable datasets generated with standardized protocol (BPOG and USP) on various single-use components has led to a deeper understanding of extractable profiles on various materials. Through a special project conducted in-house that addresses the proper way for scaling extractables in biocontainer, we share how extractable datasets can be utilized to support risk assessment of a real-case multicomponent single use system.

In addition, the expectations from Biopharm end-user and related guidance has evolved quickly in recent years, we illustrate how these complex extractable datasets impact the amount of work required for end-users’ toxicological risk assessment when comparing recent data sets and legacy extractable data.

Lastly, experiences and feedback sharing as to where end users have been successfully satisfied their regulatory obligations using such these data and where the gap remains.

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