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PharmaED's

Extractables & Leachables 2011

Strategies to Ensure Safety and Compliance in the Packaging and Processing of Drugs and Biologics

OCTOBER 10-11, 2011, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

Topics to be addressed include:

- Explore Materials Used to Fabricate Container Closure Systems and the Impact on Extractables and Leachables
- E&L Considerations in the Qualification and Validation of Single-use Systems
- Development and Validation of Analytical Methods for Analysis of Organic Leachables in Drug Products
- Current Extractables/Leachables Thinking: Impact on the E&L Approach of an Elastomeric Closure Supplier
- Replacement of Controlled Extraction Studies for PODP E&L Documentation
- Detection of Glass Particles, Flakes or Lamellae in Tubular Glass Vials

PLUS! In-Depth Pre-Conference Workshop:

Regulatory Considerations for Extractables and Leachables

Dennis Jenke, Ph.D, Principal Scientist, Technology Resources Division
Baxter Healthcare Corporation

Featuring Representation From:

Baxter Healthcare Corporation
Material Needs Consulting, LLC
Novo Nordisk A/S
Pall Life Sciences
Solvias AG
Vanasyl LLC
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Monday, October 10, 2011

8:00 *Registration and Coffee*

PRE-CONFERENCE WORKSHOP

8:30 **Regulatory Considerations for Extractables and Leachables**

Dennis Jenke, Ph.D, Principal Scientist, Technology Resources Division, Baxter Healthcare Corporation

It is a universal regulatory expectation that manufacturing, packaging and delivery systems used with pharmaceutical agents and finished products be suitable for their intended use. Among the several dimensions of suitability for use, safety is an important, and perhaps the most widely studied, consideration that must be effectively addressed for finished products to be registered and marketed. This presentation uses the relationship between the processes of product development and safety assessment to develop a "cradle to grave" strategy for addressing safety issues associated with the use of plastic systems with pharmaceutical products. The presentation considers two major questions; "what do we have to do?" and "when do we have to do it?" Both strategic and tactical issues with respect to chemical safety assessment will be considered and central points will be illustrated via the use of case studies. Essential background information which establishes a firm foundation for chemical safety assessment will be augmented by a discussion of up to the minute developments occurring within organizations that are active in this field.

About your workshop leader:

Dr. Dennis Jenke is a Principal Scientist in the Technology Resources Division of the Baxter Healthcare Corporation. In this role, he works with a team of analytical chemistry professionals whose primary responsibility includes the development, validation and application of diverse analytical strategies and methods for the discovery, identification and quantification of trace constituents in pharmaceutically relevant solutions and samples. Foremost among these applications is the assessment of material/product compatibility, specifically with respect to leachables/extractables and product ingredient binding. He has published extensively in the areas of analytical chemistry, environmental science and material/solution compatibility and serves as an expert reviewer for numerous pharmaceutical and analytical journalsis a member of industry groups whose charter is to establish best demonstrated practices in the area of material/solution compatibility and is a frequently invited speaker on the subject of material/solution compatibility. He is the author of a book entitled "Compatibility of Pharmaceutical Solutions and Contact Materials; Safety Considerations Associated with Extractables and Leachables", the sole definitive text on this subject.

12:00 *Luncheon*

1:15 **Materials Used to Fabricate Container Closure Systems and the Impact on Extractables and Leachables**

Michael A. Ruberto, President, Material Needs Consulting, LLC

Components of container closure systems and medical devices can be fabricated with a wide variety of materials. Polymers, such as plastic or elastomers (rubber), are commonly used in these applications and represent a very broad class of compounds with many different properties that can provide functionality, security, or aesthetics to the primary packaging. Plastic components are light-weight, flexible, and often more durable than traditional metal or glass and can be modified by the addition of polymer additives to have many of the desirable properties of these conventional materials such as strength and clarity. Although polymers appear to be the material of choice for use in container closure systems and have many advantages over metal and glass, they are not without shortcomings of their own. In the presence of light, heat, oxygen, and other environmental factors, polymers will degrade. Additives and stabilizers commonly added to these polymer systems to minimize this degradation can be sources of leachables, especially if they are not compatible with the polymer. This presentation will provide an overview of the issues associated with the materials used in the construction of container closure systems with regards to extractables and leachables. Topics covered will include:

- An introduction to polymer degradation and stabilization
- Typical extractables profiles for the materials used in container closure systems
- The polymer supply chain and sources of unexpected leachables
- Considerations for managing and minimizing the risk associated with material selection

2:00 **Development and Validation of Analytical Methods for Analysis of Organic Leachables in Drug Products**

Kurt Moyer, PhD, Director of Research, NSF Pharmalytica

Once extractables have been identified following the forced extraction studies, analytical methods for detection of these potential leachables in the drug product.

If a variety of extractables were observed, GC, HPLC and ICP-MS methods may be needed. Selection of detection is based upon the observed extractables and confidence in the extractables profile. If the AET requires the detection of the method to be below 0.05% of the drug, sample extraction techniques to remove the drug may be necessary. Once method development is complete, the method is validated for accuracy, precision, linearity, sensitivity (LOD/LOQ), specificity, and ruggedness. Acceptance criteria need to be appropriate for target levels for analysis, the known performance of the method and the intended used of the method. Additional strategies to improve method performance during leachables testing will be discussed as well as presentation of examples

2:45 **Current Extractables/Leachables Thinking: Impact on the E&L Approach of an Elastomeric Closure Supplier**

Renaud Janssen, Ph.D., Global Director of Scientific Affairs, Helvoet Pharma

Several collaborate projects like PQRI/OINDP, PQRI/PODP, ELSIE, IPAC-RS, ... in recent times have given a boost to the thinking related to extractables and leachables. This evolution evidently has an impact on the practices of manufacturers of primary packaging materials. Manufacturers of the latter materials are compelled to deepen the knowledge on the materials they bring to the market and to adjust their approach in putting together the extractable data packages they offer to their customers. This presentation illustrates how an elastomeric closure manufacturer responds to this evolution and how he aligns his approach with current thinking. At the same time a case study is given of how a forced material change is being handled in terms of extractables documentation.

3:15 ***Refreshment Break***

3:30 **The Simulation Study – The Replacement of Controlled Extraction Studies for PODP E&L Documentation**

Carsten Worsøe, Senior Research Scientist, Novo Nordisk A/S

During the PQRI PODP E&L workshop Feb. 2011 the AAT (Analytical Applicable Threshold) and safety assessment triad was introduced by the chemistry group to overcome the dilemma of having fixed toxicological values for large volume parenterals which will result in analytical levels that can not be met by analytical chemistry. The safety assessment triad introduces the term "simulation study" as an approach to close the gap between controlled extraction studies and long term leachable studies. The presentation will elucidate why this procedure can be used for both small and large volume parenterals and why it is even more valuable adding compared to controlled extraction studies when the goal is to get the long term leachable profile. The simulation study can fundamentally be regarded as either a simulated extraction study or as an accelerated leachable study. By introduction of an accelerated leachable study at an early development phase the risk of having critical interactions between leachables and the drug or formulation components will be observed prior to the long term leachable testing and thereby minimizing the risk for critical findings at a late phase development time point. The presentation will also describe how an accelerated leachable study can be performed for both soluble and lyophilized drug products. The presentation will furthermore describe cases of actual accelerated and long term leachables studies and how the results of such studies can be correlated.

4:15 **Manage Extractables and Leachables Resulting from Packaging Materials, Closures and Excipients**

Patty Kiang, PhD,
Kiang Consultant Services

The recent news concerning the Taiwanese and Chinese DEHP-tainted food products and leachable plasticizers from various plastic containers have raised public awareness of potential toxic leachables issues.
A screening procedure should be set up for all pharmaceutical and food container/closure systems as well as drug and food recipients

Based on the extractable data, identify and define the toxicity levels of the extractable compounds, set up the specifications for each compound and monitor the compounds from incoming raw material batches, once the process is under control, the sampling frequency can be reduced.
A detailed management and monitoring plan will be discussed in the presentation

5:00 ***Close of Day One***

Tuesday, October 11, 2011

8:30 *Chairperson's Day Two Opening Remarks*

8:45 **Low Extractable Rubber Closure: Migration Study**
Nicolas Gallois, Analytical Chemistry Engineer, STELMI

Extractables studies on primary packaging for parenterals are performed to anticipate the compatibility studies with the drug. When regulatory information according to the pharmacopoeias is insufficient, some specific extractables studies are to be performed. These studies will identify the substances which will potentially migrate from the rubber closures to the drug, using appropriate protocols. While extractables studies generate data on the substances which will migrate under exaggerated conditions of time and temperature, migration studies are designed to be more relevant for the substances that will migrate under conditions close to the drug product's normal conditions of use.

The presentation will describe the potential extractables from rubber stoppers and the general analytical methods to characterize these substances. Results of a migration study will be presented, showing that a stopper produced with a high purity rubber formulation exhibits a very low level of extractables, which may even be lower than the extractables level of an available coated rubber stopper.

9:30 **Qualification and Validation of Single-use Systems (SUS): Extractables/Leachables**
Weibing Ding, Pall Life Sciences

Single-use systems have been increasingly used in biopharmaceutical manufacturing processes. Despite their multitude of advantages, these plastic and elastomeric assemblies also draw concerns about chemical compounds that may migrate from them into finished products and impact product quality or safety. Evaluation of such extractables/leachables (E/L) and their potential impact remains a challenge to many suppliers and end users. This presentation will elucidate the practical and science-based approach developed by Pall based on extensive experience, industry group recommendations and FDA/EMA guidance.

Generic extractables data is used as part of qualification of SUS. For each biomanufacturing process, a process- and product-specific extractables and possibly leachables studies are performed as part of process validation. This includes risk assessment, test solvent assignment, test system design, test conditions selection, extraction sample analysis, and interpretation of test data through toxicological assessment. A case study will be presented. This risk-based approach has enabled single-use system users to obtain relevant and useful E/L data for toxicological assessments accepted by health authorities. This approach also minimizes project time and cost for E/L data from single-use systems.

10:15 *Refreshment Break*

10:30 **Durability of Glass Vials - Do Extractable Levels Predict Delamination?**
Dr. Michael N. Eakins, Principal Consultant, Eakins and Associates

A number of lots of several parenteral products have been been withdrawn in 2010 and 2011 due to the detection of glass particles, flakes or lamellae in tubular glass vials. The presentation looks at factors that can affect the formation of glass particles and lamellae including manufacturing parameters to produce tubular vials and the effect of the drug product formulation. The current Pharm. Eur. and USP chapters on glass containers have a surface glass test that measures the release of alkali after autoclaving with water. The presentation will discuss whether this test is sufficient to predict the likelihood of delamination or should additional, more predictive tests be employed.

11:15 **Gamma Versus Steam: Does Sterilization Make An Impact On Extractables And Performance?**
Andrea Straka, Technical Account Specialist, WEST Pharmaceuticals

Elastomeric container closures are complex mixtures of polymer, curing agents, reinforcement minerals, and more, which are expected to perform under a myriad of conditions just to bring them to the form where they can be used for a pharmaceutical packaging system. To render them sterile for entry into filling, we must put them through more rigorous processing.

Gamma, Steam, E-beam, EtO, are all techniques that have been used to attempt to sterilize elastomers with varying success. Gamma irradiation is a widely used technique for sterilization of prefilled syringe pistons; however, it is a high energy process that in theory could affect the characteristics and extractables of the closures that are in intimate contact with the drug. This presentation will examine the effects of the sterilization techniques commonly used to process prefillable syringe components and how choosing the right sterilization process can have a positive effect on the leachable profile of the final drug product.

12:00 *Luncheon*

1:30 **How Do We Ensure Material Quality for OINDP?**
Bobbijo Redler, Merck & Company

The IPAC-RS OINDP Materials Working Group is working with the OINDP container closure system (CCS) and device component supply chain to develop best industry approaches to managing the quality of component materials. The Materials Working Group has focused on the technical aspects of enhancing quality, e.g., extractables testing, pharmacopoeial requirements, certification requirements, shelf-life. The group has organized forums with suppliers, OINDP developers and manufacturers, and regulators on ways to improve the application of testing and the communication of technical information throughout the supply chain. The CCS/device supply chain is highly complex, involving a number of different suppliers, including those providing raw materials such as resins, those providing specific additives such as colorants and antioxidants, to those supplying the final CCS and device components, and the Working Group strives to connect with all of these entities. The complexity of both the supply chain and regulatory requirements necessitates a clear description of baseline requirements to ensure the quality of materials for CCS and devices.

The Working Group has developed a document describing baseline requirements for materials quality. The Group has discussed and revised the document with input from suppliers from various points in the supply chain (e.g., raw materials, converters). The document addresses expectations and timeframes for materials supply, the need for Controlled Extraction Studies, compendial testing, and certification requirements, and other topics relevant to materials quality. The document serves as a general guide for suppliers and developers to the OINDP industry, and recognizes the need for specific requirements to be worked out between suppliers and customers where necessary, with the goal of enhancing the quality and safety of drug products for patients. The presentation will highlight specific aspects of the document and discuss next steps for the Working Group.

2:15 **High Throughput Screening - An MS Based Approach For Extractables & Leachables Studies**
Dr. Karl Abele, Solvias AG

Many laboratories offer Extractables & Leachables Screening based on information received from the manufacturers regarding their specific polymers and the additives contained. This classical approach has high probability of missing impurities or unexpected additives (including their degradation products) not contained in the information received from the polymer manufacturers. Our approach takes advantage of the improvement of MS instrumentation in the last years. We use state of the art LC/MS equipment, with mass accuracies better than 3.0 ppm over a wide concentration range.

Data analysis is automated, using our proprietary additives data base (Solvias E&L 11.6), containing more than 3000 high mass accuracy LC/MS and LC/MS/MS spectra of polymer additives and their breakdown products.

- Size of the data base ensures a high percentage of compounds detected can be identified and is thus accessible for toxicological evaluation.
- Compounds identified are semi-quantified against a series of the most common additives (measured as external standards).
- Automation of data evaluation provides a constant and reproducible quality of screening results produced.

Data from LC/MS screening are being routinely compared to GC/MS based semiquantitative screening methods, which are capable of automated non-target screening up to a molecular weight of 700 amu.

Complementary evaluation of GC/MS and High Mass Accuracy LC/MS/MS data increases confidence in identifications achieved, thus providing quick and reliable results for our E&L Studies. The presentation will demonstrate the versatility of our approach using practical examples from several projects.

3:00 *Refreshment Break*

3:15 **Simplifying The Issue of Extractables And Leachables in Single-Use Components**
Tamara Fridman, Director, Vanasyl LLC

Extractables and leachables of single-use/disposable components is often an issue that end-users get stuck on. How much is too much testing? How little is too little? What information should end-users be paying attention to? How can suppliers help? How can end-users generally better understand this whole concept?

This talk is meant to simplify the issue. Whether you are a toxicologist, a chemical engineer, a process engineer, or solely from the corporate office of any pharmaceutical and biopharmaceutical companies, you will learn how to work through what seems to be a murky issue and receive 'best approach' ideas to learn the most about extractable and leachable concerns so you can have satisfactory results with your use of single-use and speed up your drug discovery and development.

4:00 *Close of Conference*

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