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Extractables & Leachables 2008

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

OCTOBER 20-21, 2008, SHERATON LA JOLLA HOTEL, LA JOLLA, CA

Featuring Case Studies and Lessons Learned from Industry Experts!

- **Examine Best Practices for Extractables and Leachables and Assess and Manage Risk**
- **Determine Suitability for Use in Extractables/Leachables Assessments**
- **Manage Extractables and Leachables Resulting from Packaging Materials, Closures and Excipients**
- **Determine Extractables and Leachables from Disposable Single Use Manufacturing Systems**

In-Depth Pre-Conference Workshop:

Extractables and Leachables: A USP Perspective

Eric B. Sheinin, Ph.D., Sheinin & Associates;

Former USP Chief Science Officer and

Ex-FDA Deputy Director, Office of Pharmaceutical Sciences

Featuring Representation From:

Helvoet Pharma

Merck & Company

Pall Life Sciences

Metron Technologies

Northup Regulatory Toxicology Services

West Monarch Analytical Laboratories

Jazz Pharmaceuticals

Pfizer, Inc.



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Monday, October 20, 2008

8:45 *Chairperson's Welcome and Opening Remarks*

PRE-CONFERENCE WORKSHOP

9:00 **Extractables and Leachables: A USP Perspective**

The regulations at 21 CFR 314.50 (d)(1)(ii)(a) require a new drug application to include specifications for the container closure system. Further, the GMP regulations at 21 CFR 211.94(a) state that containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements. The CDER Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics discusses the recommended extraction studies in Appendix C. Reference is made in this guidance to a number of general chapters found in USP-NF including <87>, <88>, <381>, and <661>. The latter general chapter has been revised recently and the sections related to glass containers moved to a new general chapter <660> Containers Glass. This presentation will include a general discussion of the relationship between the USP and the FDA, including the legal recognition; an overview of the USP perspective with regard to extractables and leachables; and a more detailed discussion of the revised <661>.

Attendees will have a better understanding of the compendial revision process, the legal recognition of the standards contained in USP-NF, and the compendial requirements with regard to testing for extractables and leachables in container closure components.

About your workshop leader:

Eric Sheinin is the president of Sheinin and Associates, consultants to the pharmaceutical industry specializing in the chemistry, manufacturing, and controls and regulatory areas. Dr. Sheinin most recently served as USP's vice President for the new Pharmaceutical Ingredient Verification Program and was responsible for developing and implementing the verification and qualification aspects of the program. The program includes drug substances and excipients. Dr. Sheinin's previous positions with USP include Chief Science Officer and Vice-President, Standards Development with responsibility for the content of USP-NF.

Dr. Sheinin previously spent 30 years with the Food and Drug Administration (FDA), most recently serving as Deputy Director, Office of Pharmaceutical Science in FDA's Center for Drug Evaluation and Research. He

served as director, Office of New Drug Chemistry from 1996-1999, and in supervisory and research chemist positions at FDA sites in Maryland and Washington, D.C. between 1971 and 1996. Dr. Sheinin also had a 16-year history of service with USP as an elected Committee of Revision (now Council of Experts) member from 1985 to 2001. Dr. Sheinin holds a B.S. degree in Zoology from the University of Illinois and a Ph.D. in Chemistry from the University of Illinois at the Medical Center in Chicago.

12:00 *Luncheon*

TOXICOLOGY CONSIDERATIONS

1:30 **Toxicology Issues on Extractable and Leachable Chemicals from Packaging Materials**

Sharon J. Northup, PhD, DABT, Northup Regulatory Toxicology Services

Container and labeling materials used in pharmaceutical packaging are often the same or similar to materials used as food product containers. Polymer formulations generally utilize low molecular weight additives such as antioxidants and stabilizers. Identified extractable and leachable from a pharmaceutical container may be intact additives or a degradant of an additive. In general, extractable and leachable compounds are classified as impurities. The most common methods of evaluation are described in the International Conference on Harmonization guidance, Impurities in New Drug Products. Additional purity criteria are found in pharmacopeial compendia such as USP <1086> Impurities in official articles <466> Ordinary impurities and <467> Organic volatile impurities (a.k.a. Residual solvents). Additional guidance is published in the International Standards Organization documents including ISO 10993-17: Establishment of allowable limits for leachable substances.

Toxicological assessment relies on published data of the parent compound(s) in the packaging formulation as well as any degradation products, if applicable. Citation of the parent compound in food packaging regulations establishes a history of human use and exposure. A literature review and toxicological evaluation and risk assessment of the extractable or leachable compound(s) would include data on single, multiple and chronic toxicity studies as well as special toxicity studies (reproductive toxicity, genotoxicity, immunotoxicity, carcinogenicity, etc.). A risk assessment of these data is essential for establishing residue limits for E&Ls in the commercial

product. This presentation will emphasize numerous guidelines and methodologies for risk assessment along with case studies.

2:30 **Toxicology Issues in Extractables and Leachables**
William P. Beierschmitt, Ph.D., D.A.B.T., Associate Research Fellow, Drug Safety Research and Development, Pfizer, Inc.

An essential, critical component of the registration package for a parenteral product that is addressed by the toxicologist is the risk assessment of extractables and leachables. From a toxicology perspective, while extractable data can provide valuable information (i.e. what chemicals might migrate into the drug during storage), formal risk assessments are typically only performed on leachables (i.e. what chemicals did migrate into the drug during storage). The basic premise of this procedure is to assess the potential risk to humans resulting from unintentional exposure to the chemicals that migrate into drug product from packaging. For each chemical, after determining the maximum potential dose a human might receive, the toxicologist uses available toxicology data, including experimentation if needed, to assess the potential risk. The route of administration and duration of potential exposure are just two of many factors taken into consideration when a risk assessment is performed. Overall, involvement of the toxicologist in extractable and leachable studies from the earliest experimental planning stage through the data collection greatly facilitates arriving at a timely and successful assessment of these chemical impurities. While there are no formal regulatory guidelines currently in place addressing the risk assessment of these impurities, safety thresholds for risk assessment of leachables in orally inhaled and nasal drug products (OINDP) have been developed through a joint effort of scientists from the US FDA, academia and industry, and such thresholds will greatly facilitate the risk assessment process for these chemicals. This lecture will provide an overview of current and future concepts in the risk assessment of extractables and leachables in parenteral products.

3:30 *Refreshment Break*

CONTAINER CLOSURES

3:45 **Extractables and Leachables From Elastomeric Closures for Parenteral Applications**
Douglas Cusato, Technical Support Manager, Helvoet Pharma
Currently one of the most highly pursued topics in the

parenteral closure arena is Extractables and Leachables. Two of the main reasons are toxicological, and drug stability concerns. To minimize the occurrence of these problematic issues, supplier and pharmaceutical companies invest endless amounts of time and resources into identifying and validating techniques to detect extractables and leachables. With respect to elastomeric closures, the most widely researched extractables and leachables are accelerators (carcinogenic nitrosamine substrates and cytotoxic molecules), volatiles (alkanes, oligomers and aromatics), carbon black waste (polynuclear aromatic hydrocarbons), and antioxidants (mostly BHT and Igranox).

As chromatographic databases of extractables and leachables from elastomeric components begin to develop, the sources, impurities, degradation and feasible mechanisms have become of great scientific interest. Within this presentation, attempts will be made to discuss topics and define industry questions related to the subject of extractables and leachables with regards to:

- Actual definitions
- Sources of extractables and leachables
- Associated impurities and degradation products
- Elastomeric Closure Supplier Support

4:45 *Close of Day One*

Tuesday, October 21, 2008

8:45 *Chairperson's Day Two Opening Remarks*

INJECTABLES CONSIDERATIONS

9:00 **Extractables and Leachables for Injectables: Regulatory Issues and Best Practices**
Andrea Straka, Technical Account Specialist, West Monarch Analytical Laboratories

Over the last decade or so, issues with leachables in pharmaceuticals have created concern within the industry. With instrumentation becoming more sensitive and drug products becoming more potent, and formulations becoming more complex, leachables and extractables have risen to be front burner issues.

This session will:

- Summarize the current regulatory requirements in the US and in Europe

- Present best practices for studies involving injectable and liquid products
- Discuss how industry groups such as PQRI and IPAC-RS are responding to the issues
- Review case studies that show the presence of leachables in marketed drug products

SINGLE USE SYSTEMS

9:45

BPSA Recommendations for Determining Extractables and Leachables from Disposable Single Use Manufacturing Systems

Jerold Martin, Sr. V.P. Scientific Affairs, Pall Life Sciences, and Director and Chair, Technology Committee, BioProcess Systems Alliance

The use of disposable single-use systems for the manufacture of biopharmaceuticals and pharmaceuticals is a growing trend. In 2006, several equipment suppliers formed the Bio-Process Systems Alliance (BPSA) to help users understand the benefits of single use manufacturing as well as the validation requirements for single-use systems. Among its' activities, BPSA has published a series of articles with Recommendations for Extractables and Leachables Testing of single use process fluid-contact systems. The methods to address extractables and leachables from process contact equipment are similar to those for final container/closure systems, however, there are some key differences based on the level of safety and regulatory risk associated with their use. This presentation will highlight the regulatory requirements and BPSA's recommended approach for suppliers and users to address extractables and leachables from single use process contact equipment.

- Understand how to assess the risk associated with the use of a single use disposable manufacturing system with regard to extractables and leachables
- Work better with suppliers to obtain extractables data
- Outline when and how to test for extractables and leachables from process equipment

10:45 *Refreshment Break*

Extractables/Leachables from Integrated Single-Use Systems in BioPharmaceutical Manufacturing

Weibing Ding, Ph.D., Technical Manager, Pall Life Sciences

There are a multitude of advantages to single-use

technologies for biopharmaceutical manufacturing. However, more than their stainless steel counterparts, single-use systems draw concerns about extractables and leachables from organic-based plastics and elastomers from which some compounds may migrate to finished products. Therefore, it is imperative to develop a suitable method to study extractables/leachables from single-use systems.

This talk presents a systematic study of extractables from single-use systems into water and ethanol via novel concepts, practical design, and analytical detection using advanced techniques. In order to tackle the fairly complex systems, we studied the components first, which included filters, connectors, and biocontainers, and then examined the whole single-use systems comprised of filter, tubing, connectors, and biocontainers. This approach greatly simplified the identification of the extractable compounds from the whole systems. The test design was based on actual process conditions using a worst-case scenario. The complete extractables results were obtained using validated analytical methods, including non-volatile residue measurement and FTIR for qualitative assessment, GC/MS for volatile/semi-volatile compounds, derivatization GC/MS for organic acids, HPLC/UV, LC/MS and LC/MS/MS for nonvolatile and heat-sensitive compounds, and ICP/MS for inorganic elemental analysis.

1. Know how to design extractables/leachables study for single-use systems (Rationale: The idea of performing studies on components first, and then on complex system is new and effective; the unique test design is practical. The test design can be adopted by the audience for their own studies).

2. Know how to utilize the modern analytical techniques for identification and quantification of extractables/leachables from single-use systems (Rationale: Detailed examples on GC/MS and LC/MS studies will teach the audience about the selection of right instrument for different types of compounds, and what kinds of compounds will be extracted out).

3. Understand what active roles the suppliers can play in the extractables/leachables field (Rationale: Suppliers can be proactive and study extractables/leachables from their products based on actual/potential applications).

4. Know a source that can help to perform extractables/leachables study and/or validation of single-use

systems (Rationale: There are few good approaches for single-use systems study. This serves as a good example and could be incorporated into standard industry practice).

12:00 Luncheon

IMPURITIES IN EXCIPIENTS

1:30

Strategies for Handling Impurities in Excipients: Strategies for Identity and Control

Sreevalsan Divakar, Senior Scientist, Quality Sciences Department, Jazz Pharmaceuticals

Traditional approach of considering excipients as a relatively marginal to the main business of producing blockbuster active ingredients is changing rapidly under the pressure of evolving regulatory guidelines. Therefore, better control of excipients becomes a regulatory and business need for advancing fast drug development plans and getting trouble free approvals. Systematic approach in identifying the correct excipients, understanding its manufacturing process and knowledge about its impurity profile will help the Pharmaceutical Scientist to design a drug development plan to meet the stringent timelines of the management and business needs of the industry.

Evaluation and identification of impurities present in the excipients and the technical information about the potential degradation products generated from the excipients during its shelf life and their (degradation products of excipients) chemical interaction with the Drug Substance will definitely be an added advantage in understanding the degradation profile of drug product in early development stages like Pre-IND and Phase I. This topic will also cover the source of impurities in excipients, types of impurities expected in excipients including residual solvents, and the effect/influence of process parameters in manufacturing excipients. In addition to the above, following topics will also be discussed:

- Business strategies in getting complete information about the excipients in use
- FDA, ICH and USP Approaches to the control of impurities
- Process related impurities in excipients
- Genotoxic impurities in excipients
- Residual solvents in excipients
- Excipients compatibility study in drug development program
- Analytical tools to identify impurities in excipients
- Evaluating excipients related compounds (impurities?) in stability studies

2:30

DATA COLLECTION STRATEGIES

Strategies for Identifying Low Level Compounds

Peifeng Hu, Baxter Healthcare Inc.

A critical aspect for leachable/extractable study is to be able to identify unknown compounds at very low levels. The first challenge is to acquire data at the required levels. Very often the best one can do is the acquisition of incomplete set of data or data of limited quality. The second challenge is then how to extract and utilize information from limited amount of data to derive structures. This presentation will examine ways to maximize data acquisition and to use the data to the fullest extent.

The following topics will be discussed:

- What is special about trace level compound identification
- Data dependent experimental design
- Non-laboratory tools
- Lessons learned from real life issues and case studies
- General approaches

3:15

Refreshment Break

3:30

Leachable Study on Solid Dosage Form

Xueguang Fang, Scientific Fellow, Merck & Co.

ICH requires that impurities and degradates be monitored for pharmaceutical products. A study was undertaken to further understand potential extractables/leachables which could be derived from common pharmaceutical packaging materials. The leachable components were identified as photoinitiators: 1-Benzoylcyclohexanol and 2-Hydroxy-2-methylpropiophenone, by comparing UV, GCMS, and LCMS data with the authentic samples. The study clearly demonstrated that the photoinitiators are able to leach from the label containing them and penetrate the HDPE wall under stressed conditions.

- Identify the Unknown peak by using UV, GCMS and LCMS technology
- Determine whether the photoinitiators may be able to migrate through the HDPE wall
- How to use the RRF to adjust the results for safety concern of the photoinitiators.

4:15

Interactive Panel Presentation

5:00

Close of Conference



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