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# Impurities Forum 2007

*Strategic Identification and Detection, Control and Methods to Ensure Regulatory Compliance for APIs and Drug Products*

SEPTEMBER 10-11, 2007, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

**Featuring Case Studies and Lessons Learned from Industry Experts!**

- Examine FDA, ICH, and USP Approaches to the Control of Impurities
- Choose and Evaluate Tools for Impurities Identification
- Genotoxic Impurities: Understanding the Additional Challenges Posed
- Using Chromatography and Mass Spectrometry to Identify Impurities
- Strategies for Residual Solvents Testing and Methods Validation

**Extractables and Leachables Coverage!**

**Toxicology Considerations and Risk Assessment Strategies  
Strategies for Identifying Leachables and Impact of Photoinitiators  
Determining Leachables Using HPLC Multi-Detection Systems**

**Featuring Case Studies From:**

Bristol Myers-Squibb  
Baxter Health Products  
Sheinen & Associates  
KOS Pharmaceuticals

Pfizer Global Research and Development  
West Pharmaceutical Services  
Lancaster Laboratories, Inc.  
Northrup Regulatory Toxicology Services

Merck & Co., Inc.  
Patheon, Inc.  
Ilypsa, Inc.  
Helvoet Pharma Inc.



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**Monday, September 10, 2007**

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

## **SPECIAL IN-DEPTH REGULATORY SESSION!**

9:00 **FDA, ICH, and USP Approaches to the Control of Impurities**

***Eric B. Sheinin, Ph.D., Sheinin & Associates; Former USP Chief Science Officer and EX-FDA Deputy Director, Office of Pharmaceutical Sciences***

ICH has completed three Guidelines dealing with the control of impurities in new submissions to regulatory authorities for market approval in the three ICH regions. The U.S. Food and Drug Administration has extended the principles of these Guidelines to applications for generic drugs in addition to applications for drug not currently legally marketed in the U.S. The USP has proposed revisions to General Chapter <467> Organic Volatile Impurities to bring it into conformance with ICH Q3C. USP also has initiated a new approach to the control of impurities in official articles to conform with Q3A and Q3B. How the FDA, ICH, and USP approaches agree and differ is the topic of this presentation. What does this mean to the pharmaceutical industry?

### ***About your session 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.

10:45 *Refreshment Break*

## **IMPURITIES IN EARLY DEVELOPMENT**

11:00 **Determination of Related Substances in Pharmaceutical Articles During Early Development**

***Dr Geoff Carr, Director, Analytical Development, Patheon Inc.***

It is very important to begin to understand the related substances profiles of pharmaceutical articles even at the earliest stages of development programs. This is necessary to ensure that we are meeting the requirements for impurity qualifications as set out within the Q3A and Q3B ICH Guidelines. The challenge is that suitable analytical methods need to be developed and appropriately validated when it is quite likely that we do not yet know the nature of the impurities that require monitoring. This presentation will discuss likely sources of impurities and why it is that we don't know what we are looking for. It will then go on to suggest approaches for dealing with this so that the analytical development program is designed to evolve through development and systems are established to re-evaluate earlier batches as new information about impurities is collected. As impurity profiles become more established, the approaches to quantification also evolve and this needs to be addressed within analytical methods validation programs. Finally there will be some discussion on additional challenges presented by potential genotoxic impurities.

- Understanding the challenge to establish knowledge of impurity profiles very quickly to enable rapid drug development when we don't know what impurities are likely to be present
- Monitoring impurities that arise from synthesis
- Developing knowledge of degradation chemistry by conducting stress studies
- Approaches for dealing with chiral impurities
- Conducting appropriate validations as related substances methodologies evolve
- Developing related substances specifications during early development
- Additional challenges of potentially genotoxic impurities

11:45 Luncheon

1:15 **Challenges of Identification of Impurities in Early Development**

**Sreevalsan Divakar, Senior Staff Scientist, Analytical Sciences Dept, Ilypsa Inc, CA**

The Food and Drug Administration (FDA) requires drug manufacturers to identify, quantify and monitor impurities in API and Drug Product. Sources of these impurities are not just limited to degradation products and that inherent to the API. Investigation of impurities must be carried out at earlier stage of drug development (i.e. pre IND stage). Source of impurity in the final API/Drug product may be residual starting materials, impurities and degradation products of starting materials, process impurities, inorganic impurities from catalyst, potential known and unknown degradation products. Strategy to identify the potential impurities in the early stage will help the drug manufacturer to speed up the drug development process and the increasing need to identify impurities quickly, to select efficient test procedures offers continuing challenges for the Chemist, including maintaining awareness of rapidly evolving regulatory needs. The following key aspects of identification of impurities in early development will be illustrated:

- Strategies for identification of impurities in early development
- Source of impurities from starting materials (residual starting materials/imps of starting material)
- Process impurities
  - Catalyst related
  - Residual solvents
  - Synthetic impurities
  - Degradation products
  - Regulatory requirements
  - Analytical tools
  - Minimization/Elimination
  - Acceptance limits

2:00 **Finding the Proverbial Needle in the Haystack: Identification and Monitoring of Impurities in Pharmaceutical Ingredients and Drug Products Using Chromatography and Mass Spectrometry**

**John L. Snyder, Principal Scientist, Method Development and Validation, Lancaster Labs, Inc.**

The monitoring and identification of impurities in pharmaceutical products and drugs is extremely important

to insure the safety of the consumer. The use of mass spectrometry coupled with a chromatographic separation can often provide a method for monitoring or identifying impurities. However, many times the chromatographic method that first detects the impurity is not compatible with the mass spectrometer. Often the impurity is very small in relation to the active pharmaceutical ingredient (API) and the other excipients present in the sample. In this presentation several case studies using mass spectrometry coupled with a chromatographic separation to either monitor a known impurity or identify an unknown impurity will be presented. In the first example, a method using liquid chromatography and tandem mass spectrometry (LC/MS/MS) was used to monitor the "clearance" of tetracycline from a variety of protein process streams during the manufacture of therapeutic proteins. During the validation of this method a detection limit of approximately 100 ng/g was demonstrated for the tetracycline in relation to the protein concentration and recoveries greater than 70% were achieved on spiked samples. In the second case study, headspace sampling and gas chromatography mass spectrometry (HS/GC/MS) was used to qualitatively identify an unknown peak observed in a chromatogram of a drug substance generated using gas chromatography with flame ionization detection (GC/FID). The peak was identified as chloroethane from its spectrum and was traced to the reaction of dimethylsulfoxide (DMSO) that used as a vehicle in headspace analysis and the hydrogen chloride present in the drug substance. In the last example, accurate mass measurements were made using liquid chromatography and a time of flight mass spectrometry (TOFMS) to determine the source of an unknown peak observed in the UV chromatogram of a steroid-coated implantable device. The source was traced to polyurethane tubing used in the manufacture of the device.

- A simple clean up step for protein matrices.
- Monitoring of antibiotic impurity using LC/MS/MS and multiple reaction monitoring.
- Headspace sampling and GC/MS analysis of volatile residual solvents.
- Techniques to make chromatographic methods compatible with LC/MS.
- Fraction collection of impurity peaks.
- Use of accurate mass measurement to identify unknown impurities.

2:45

*Refreshment Break*

3:00 ***Development, Validation and Use of Residual Solvent Methods***

***Edward Szczesny, Manager, Global Stability, Pfizer Global Research and Development***

The level of residual solvents, used in most pharmaceutical processing steps, must be determined and controlled. They are considered to be impurities that may impact manufacturing, stability and safety of pharmaceuticals. Methods for testing residual solvents, and the degree of validation for these methods will be discussed.

## ***IN-DEPTH CASE STUDIES!***

4:00 ***It's a New Impurity! Isolating and Identifying Process Related Impurities in Drug Development***

***Terri Natishan, Senior Investigator in the Analytical Development, Merck & Co., Inc.***

New impurities can appear suddenly in drug development due to changes in the synthetic process or starting materials. The challenge to manage and control formation of new impurities has been made even greater by the use of outsourced key intermediates in drug substance processes. This presentation will provide real case studies which will detail the techniques used to isolate and identify new impurities which occurred in late stage drug development. The purification approaches by semi-preparative chromatographic methods will be described to rapidly isolate impurities for spectroscopic identification. Highlighted will be examples of how the integration of NMR, mass spectrometry and process chemistry knowledge were used to identify the structures of the impurities. This presentation will provide guidance for the following:

- How to evaluate and choose the tools to identify low level impurities
- Determine the acceptable impurity level based on regulatory requirements
- Develop understanding of the origin of impurities from the synthetic process scheme

4:45 ***Panel Discussion Examining Current Technologies and Impurities Detection Strategies: Current Developments and Considerations***

During this interactive discussion, hear faculty members discuss new developments and technologies available that have recently changed industry approaches to impurities detection.

5:15 *Close of Day One*

**Tuesday, September 11, 2007**

## ***IN-DEPTH CASE STUDIES!***

8:15 ***Strategies for Identifying Trace Level Impurities***

***Peifeng Hu, Ph.D, Senior Research Scientist, Baxter Healthcare Inc.***

The capability to identify impurities is important throughout the life cycle of a drug. Structure elucidation for low level impurities is difficult due to challenges in obtaining quality spectroscopic data. Every case thus becomes unique. The approaches/strategies will have to be tailored for individual cases. This lecture will share some experiences in real world problem solving.

- What is special about trace level impurity identification
- Data dependent experimental design
- Lessons from real life issues - case studies
- Appropriate level of effort if not complete characterization
- General approaches

## ***GENOTOXIC IMPURITIES***

9:00 ***Examining Genotoxic Impurities***  
***W. Peter Wuelfing, Ph.D, Research Fellow, Merck & Co.***

This session will address a PhRMA white paper "A Rationale For Determination, Testing and Control of Genotoxic Impurities in Pharmaceuticals" from an analytical chemist's perspective and how these principles can be viewed in relation to ICH non-genotoxic impurity guidelines in formulation and API development. Among the issues to be addressed include:

- A breakdown of the white paper's risk based approach to exposure levels that scale with time of dosing in clinical trials
- How these scales exposure levels can be larger than existing ICH non-genotoxic limits in certain cases and how this can open a larger dialogue
- A discussion of current business practices

9:45 *Refreshment Break*

## COMPREHENSIVE EXTRACTABLES AND LEACHABLES COVERAGE

10:00

### *Identification of Leachables and Extractables* **Rex D. Roberts, Director, Laboratory Operations, West Pharmaceutical Services**

The methods for identification of compounds that comprise potential leachables and extractables will be discussed. Identification is supported by a knowledge of the composition of the formulations used for enclosures and medical devices. Mass spectrometry and knowledge of organic chemistry continue to be the most powerful techniques for positive identification of leachables and extractables. Preparative chromatography for compound isolation and NMR for determination of structure may be needed in some cases. Specific examples showing the modern identification process will be described.

- What are the sources of leachables and extractables?
- The most powerful techniques for identification of leachables and extractables

10:45

### *Leachables and Extractables – The Toxicologist's Perspective* **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 leachables and extractables. 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, early involvement of the toxicologist in leachable and extractable studies from the earliest experimental planning stage through the data collection greatly facilitates arriving at a timely and successful

assessment of these chemical impurities. Moreover, continued improvement in communication and information exchange with manufacturers regarding constituents/chemical make up of packaging components would also facilitate the risk assessment process.

11:30

### *Leachable Studies of Single-Use Disposables Used in Biopharmaceutical Manufacturing* **Maria S. Somma, Linda A. Zitzner, and Samantha Tan, Metron Technology**

This presentation describes a case study for chemical compatibility of diverse solutions with two commercially available and two newly developed single use disposable storage bags to determine their potential to leach contaminants.

The new storage bags were compared to the commercially available bags to establish if they could be used as alternatives for drug storage by incubating them under 'worst-case' conditions in terms of storage time and temperature, composition of solutions and surface-to-volume ratio.

An overview of the analytical approach for the comparison of the four types of single use disposable storage bags and the analytical techniques used for the case study will be presented including SPME GC-FID for volatile organic compounds, solvent extraction and GC-MS for semi-volatile organic compounds and ICP-MS for trace metals. The general trends observed and the analytical results obtained will be illustrated.

12:15

*Luncheon*

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&L's in the commercial product. This presentation will emphasize numerous guidelines and methodologies for risk assessment along with case studies.

2:15

## *Exploring the Potential for Determining Leachables Using HPLC Multi-Detection Systems*

**Jim Castner, Senior Principal Research Scientist, Bristol Myers Squibb**

The most commonly used analytical technique for determining impurity levels in pharmaceutical products is HPLC. Conventionally the focus of the chromatographic method is to monitor the stability indicating compounds related to the drug substance. Besides quantitatively detecting the related substance impurities, the HPLC method has the potential of also determining leachables in the drug product. The ability of one analytical method to provide information about product stability and exposure compatibility to manufacturing equipment as well as primary packaging material affords an economy of analytical resources. In this presentation a technique is proposed for assessing, as well as developing the capability of a HPLC impurity method for detection of leachables. The technique is based upon the use of partition/distribution properties of a series of reference compounds to determine the analytical range of the

chromatographic method for this application. In this presentation the topics that will be covered are:

### I – Definition of terms

Leachable vs. Extractable

Log P vs. Log D application

### II – Risk Analysis

Regulatory perspective

Route of Administration

### III – Sources of leachable contamination

Container/Closures

Process Equipment

Sampling Devices

### IV - Analytical Techniques

Selection of appropriate detection systems

Novel approaches (Simple vs. Sophisticated)

### VI – Analytical Range criteria based upon

Formulation solubility properties

Extractable vs. Leachable profiles

### VII – Literature Resources

Published Reviews and Papers

Computer programs

3:00

*Refreshment Break*

3:15

## *Extractables and Leachables From Elastomeric Closures for Parenteral Applications*

**Douglas Cusato, Technical Support Manager, Helvoet Pharma Inc.**

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 elastomer 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).

The many subjects related to extractables and leachables are currently not fully defined within the pharmaceutical closure industry. These subjects include the definition of extractables and leachables, the source and methods to identify extractables and leachables from elastomeric components, and the regulatory aspects associated with extractables and leachables. The present explanation for such discrepancies is mainly caused by the lack of scientific and regulatory publications that document information and concrete guidelines.

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
- Insufficiency of compendial testing
- Elastomeric Closure supplier support
- Toxicological concerns
- Regulatory perspectives

4:00

## ***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-methylpropionophenone, 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.

This session includes:

- 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.

4:45

## ***Qualification and Control Strategies for Inhalation drug Product Packaging Components*** ***Dr. Yaping Zhu, Director, Aerosol R&D,*** ***KOS Pharmaceuticals***

Extractables from Metered Dose Inhalers (MDIs) come primarily from rubber gaskets and secondarily from plastic parts of metering valves or can liners. Compounds with known toxicity such as nitrosamines, polynuclear aromatic hydrocarbons (PNAs), and mercaptobenzthiazole, can potentially be leached into an inhalation drug product, leading to a great concern to regulators. Routine testing for component extractables is therefore required on those components which contact either the drug product and/or the patient's mucosa. This presentation will discuss how to effectively deal with extractables and leachables in inhalation drug products to ensure consistency and safety of the container closure system.

- Discuss information on sources of extractables from packaging components made from rubber, plastic and epoxy resin
- Overview of the PQRI recommendations
- Typical approaches to extractables and leachables evaluation

5:30

## ***Extractables and Leachables for Injectables: Regulatory Issues and Best Practices*** ***Andrea Straka, Technical 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, leachables and extractables have risen to more than just buzz words. This session will:

- Review some of the case studies that opened our eyes to the presence of leachables
- Discuss how industry groups such as PQRI and IPAC-RS are responding to the issues
- Summarize the regulatory requirements in the US and in Europe
- Present some best practices for studies involving injectable and liquid products

6:15

*End of Conference*



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